PREVALENCE AND FACTORS ASSOCIATED WITH SEVERE PAIN AND INADEQUATE PAIN TREATMENT, SATISFACTION WITH PAIN TREATMENT AND QUALITY OF LIFE AMONG CANCER PATIENTS RECEIVING PALLIATIVE CARE

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by

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LIST OF ABBREVIATIONS

AMM	Academy of Medicine Malaysia
APS	American Pain Society
ASEAN	The Association of Southeast Asian Nations
ASR	Age-standardized incidence rate
COX-2	Cyclooxygenase-2
CR	Controlled release
CRF	Case Report Form
EAPC	European Association for Palliative Care
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C15-PAL	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 15 - Palliative
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
ESMO	European Society for Medical Oncology
GIST	Gastrointestinal Stromal Tumor
IARC	International Agency for Research on Cancer
IASP	International Association for the Study of Pain
IBM SPSS	International Business Machines Corporation Statistical Package for the Social Sciences
IQR	Interquartile Range
IR	Immediate release
MEDD	Morphine Equivalent Daily Dose
MOH	Ministry of Health

MREC	Medical Research and Ethics Committee
MRN	Medical Record Number
NCCN	National Comprehensive Cancer Network
NGO	Non-governmental Organization
NPRS	Numeric Pain Rating Scale
NRS	Numeric Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
NSPCCP	National Strategic Plan for Cancer Control Programme
OR	Odds Ratio
PMI	Pain Management Index
PI	Principal Investigator
PROMS	Patient-reported Outcome Measures
QoL	Quality of Life
ROC	Receiver Operating Characteristic
RR	Relative Risk
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
TSQM v1.4	Treatment Satisfaction Questionnaire for Medication version 1.4
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organization

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Appendix A Ethics Approval Letter: NMRR-19-927-46270 (IIR)

Appendix B Patient Information Sheet and Informed Consent Form (English and Malay Version)

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PREVALEN DAN FAKTOR YANG BERKAITAN DENGAN KESAKITAN PARAH DAN RAWATAN KESAKITAN YANG TIDAK MENCUKUPI, KEPUASAN DENGAN RAWATAN KESAKITAN DAN KUALITI HIDUP DALAM KALANGAN PESAKIT KANSER YANG MENERIMA RAWATAN PALIATIF DI PULAU PINANG

ABSTRAK

Kesakitan sering berlaku dan membawa penderitaan kepada pesakit kanser, terutamanya di peringkat lanjutan. Penjagaan paliatif adalah penting dalam pengurusan pelbagai simptom, termasuk kesakitan, di kalangan pesakit kanser, dengan tujuan meningkatkan keselesaan dan kualiti hidup mereka. Namun demikian, data tempatan di Malaysia mengenai pengawalan kesakitan dalam kalangan pesakit kanser yang menerima penjagaan paliatif masih terhad. Kajian ini bertujuan untuk menentukan prevalen kesakitan parah dan rawatan kesakitan yang tidak mencukupi serta faktor-faktor yang berkaitan, kepuasan terhadap rawatan kesakitan dan kualiti kehidupan dalam kalangan pesakit kanser yang menerima penjagaan paliatif di Pulau Pinang, Malaysia. Kajian keratan rentas ini melibatkan 162 orang pesakit kanser yang menerima penjagaan paliatif, dari 28 Jun 2019 hingga 5 Mac 2020 di Pulau Pinang. Kaedah persampelan kemudahan digunakan dan pengumpulan data dijalankan dengan cara borang soal selidik diisi oleh penyelidik. Tahap kepuasan terhadap rawatan kesakitan dan kualiti kehidupan dinilai dengan menggunakan TSQM 1.4 dan EORTC QLQ-C15-PAL masing-masing. Daripada 162 orang pesakit, 35.8%. mengalami kesakitan parah dan 17.3% memperoleh Indeks Pengurusan Kesakitan (IPK) negatif. Skor purata (sisihan piawai) kepuasan global terhadap rawatan kesakitan adalah 61.8±16.33, dengan skor lebih rendah terhadap keberkesanan rawatan (60.1±16.77) berbanding dengan kesan sampingan (64.9±16.29) dan kemudahan dalam pengambilan rawatan (69.4±12.32). Skor purata (sisihan piawai) kualiti kehidupan global ialah 54.4±24.63, dengan kedua-dua fungsi fizikal dan emosi terjejas. Analisa regresi logistik berganda menunjukkan IPK negatif, skor kepuasan global yang lebih rendah, skor insomnia yang lebih thinggi serta interaksi antara penggunaan analgesik adjuvan dan skor kepuasan global adalah faktor-factor signifikan yang berkaitan dengan kesakitan parah, dengan nisbah ganjil 26.5 (95% CI 6.79-103.71), 0.96 (95% CI 0.93-0.99), 1.01 (95% CI 1.00-1.02) dan 1.02 (95% CI 1.01-1.04) masing-masing, selepas penyesuaian dengan faktor-faktor lain. Manakala dua variabel didapati berkaitan dnegan IPK negatif adalah skor fungsi fizikal (OR 1.02, 95% CI 1.01-1.04, *p*=0.004) dan skor kepuasan global (OR 0.96, 95% CI 0.93-0.99, *p*=0.003), tetapi keputusan ini tidak dapat memberikan kesimpulan yang pasti. Kesimpulannya, tahap pengawalan kesakitan dalam kalangan pesakit kanser yang menerima rawatan paliatif di Pulau Pinang masih boleh dipertingkatkan. Pengenalpastian golongan pesakit yang mengalami kesakitan parah dan rawatan kesakitan yang tidak mencukupi adalah penting, serta perlunya memberikan intervensi tepat pada masanya.

PREVALENCE AND FACTORS ASSOCIATED WITH SEVERE PAIN AND INADEQUATE PAIN TREATMENT, SATISFACTION WITH PAIN TREATMENT AND QUALITY OF LIFE AMONG CANCER PATIENTS RECEIVING PALLIATIVE CARE

ABSTRACT

Pain is prevalent and debilitating in cancer patients, particularly at advanced stages. Palliative care is vital in effectively managing various symptoms, including pain, in cancer patients, with the goal of enhancing their comfort and quality of life. However, local data in Malaysia on pain control among cancer patients in the palliative care setting is limited. This study aimed to determine the prevalence and factors associated with severe pain and inadequate pain treatment, satisfaction with pain treatment, and quality of life (QoL) among cancer patients receiving palliative care in Pulau Pinang, Malaysia. This cross-sectional study involved 162 cancer patients receiving palliative care from 28 June 2019 to 5 March 2020 in Pulau Pinang. The convenience sampling method was employed to recruit eligible patients. Data was collected from the patients using interviewer-administered questionnaires. Satisfaction with pain treatment and QoL were assessed using TSQM 1.4 and EORTC QLQ-C15-PAL Questionnaire, respectively. Of 162 patients, 35.8% experienced severe pain and 17.3% had negative Pain Management Index (PMI). The mean (SD) score of global satisfaction with pain treatment was 61.8±16.33, with lower scores on the satisfaction with effectiveness (60.1±16.77), compared to side effects (64.9±16.29) and convenience of the treatment (69.4±12.32). The mean (SD) score of global QoL was 54.4±24.63, with both physical and emotional functioning were negatively affected. Multiple logistic regression analysis showed that negative PMI, lower global satisfaction score, higher insomnia score, and the interaction between adjuvant analgesics use and global satisfaction score were the significant factors associated with severe pain, with odds ratios of 26.5 (95% CI 6.79-103.71), 0.96 (95% CI 0.93-0.99), 1.01 (95% CI 1.00- 1.02) and 1.02 (95% CI 1.01-1.04) respectively, after adjustment for confounding factors. Two variables, namely physical functioning score (OR 1.02, 95% CI 1.01-1.04, p=0.004) and global satisfaction score (OR 0.96, 95% CI 0.93-0.99, p=0.003) were found to be associated with negative PMI, but the results were inconclusive. In conclusion, there is still room for improvement in pain management among the cancer patients receiving palliative care in Pulau Pinang. It is important to recognize the subgroups of patients with severe pain and inadequate pain treatment, and to provide timely intervention.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

The global burden of cancer incidence and mortality is rapidly increasing. According to the recent Global Cancer Observatory Report 2020, there were about 19.3 million new cases and 9.96 million deaths due to cancer worldwide in 2020 (Sung et al., 2021). The International Agency for Research on Cancer (IARC) predicts that the number of new cancer cases will rise by 47% to 28.4 million and deaths due to cancer will increase to about 16.3 million worldwide in 2040 (Sung et al., 2021). In Malaysia, a total of 48,639 new cases was recorded in 2020 (International Agency for Research on Cancer [IARC], 2021a), and it is anticipated to double by 2040 (IARC, 2021b). In 2019, cancer accounted for 12.18% of reported deaths in Ministry of Health (MOH) hospitals, compared to 9.54% in 2004 (MOH, 2021).

The increasing trends of cancer cases and mortality pose significant challenges in managing this population especially those in the terminal stage. Literature has shown that cancer patients particularly those in advanced or terminal stage typically have a high symptom burden, with pain being one of the most common and devastating symptoms (Barbera et al., 2010; Bubis et al., 2020; Siemens et al., 2020; Teunissen et al., 2007). Palliative care services have been shown to improve symptom burden, including providing pain relief, and to enhance quality of life for these patients (Holmenlund et al., 2017; Kavalieratos et al., 2016; Yennurajalingam et al., 2011). Palliative care can be provided at any point along the cancer care, from the time of diagnosis, during treatment and till the end of life (National Cancer Institute [NCI], 2021). Palliative care has been increasingly recognized as one of key components in cancer care and the demand for palliative care services is expected to grow rapidly. World Health Organization (WHO) pointed out about 40 million people worldwide, including those with advanced or terminal cancer, require palliative care annually but it is estimated only 14% of patients receive it (World Health Organization [WHO], 2020). In Malaysia, palliative care was introduced in the 1990s and it has been preliminarily integrated into the mainstream healthcare services (Yang et al., 2022). Palliative care services are currently available in most of the major public hospitals, few private healthcare institutions and non-governmental organization (NGO) hospices across the nation (Yang et al., 2022). Palliative care is provided not only to cancer patients at advanced or terminal stages with significant symptom burden, such as pain, but also to individuals at any stage of the disease suffering from physical symptoms, psychosocial or spiritual distress (Academy of Medicine Malaysia [AMM], 2015; MOH, 2010b).

Pain is a subjective perception with a wide inter-individual variability (Fillingim, 2017; Mogil, 2021). It is also known that pain is a multidimensional and complex phenomenon resulting from the interactions of physiological, psychological, cognitive, social, and spiritual aspects (Mehta & Chan, 2008; Wool & Mor, 2005). Undoubtably, pain can impose significant negative impact on the various aspects of quality of life in cancer patients (Mystakidou et al., 2007; Rodriguez et al., 2019). Hence, comprehensive assessment of cancer related pain is important to truly understand the overall experience of pain in cancer patients. The use of patient-reported outcome is useful to identify the treatment gap and the unmet needs, which can improve the decision making and treatment planning (Dawson et al., 2010; Etkind et al., 2015; Evans et al., 2013). It is also important to recognize the risk factors associated with severe or uncontrolled cancer pain and inadequate pain treatment, as these can help clinicians to identify the high risk groups and to provide timely intervention.

Currently, there is limited documentation on the management of cancer pain among cancer patients receiving palliative care in Malaysia. Data on the epidemiology of cancer pain, treatment and its outcome is mostly derived from studies conducted in developed countries such as the United States and European countries where the palliative care is well-integrated in cancer care (van den Beuken-van Everdingen et al., 2007a; van den Beuken-van Everdingen et al., 2016). The findings from these countries may not be generalizable to local populations with different socio-cultural backgrounds, levels of palliative care development and healthcare resources. Hence, further studies are warranted to explore the current situation and the challenges in managing cancer pain among advanced cancer patients, in order to have well-defined data that can be incorporated into clinical practice.

1.2 Problem Statement

In literature and clinical practice, pain is one of most frequently reported and feared symptoms in cancer patients. Despite the advancements in pain treatment and ongoing efforts to improve pain management, numerous studies have highlighted the unsatisfactory level of pain control among cancer patients, especially those in advanced or terminal stages (van den Beuken-van Everdingen et al., 2016). In general, studies from Asian countries showed higher rate of severe pain than those from western countries. In Malaysia, data on the prevalence of severe pain among advanced cancer patients receiving palliative treatment is limited (Mansor et al., 2008; Mejin et al., 2019).

This has become an increasing concern as uncontrolled or severe pain is frequently associated with patients' compromised ability to cope with diseases (Yoong & Poon, 2018), disruption of cancer therapy (Yoong & Poon, 2018), complicated analgesic regimens (Fainsinger et al., 2009), frequent medical complications (Mystakidou et al., 2005; O'Mahonyet al., 2005), treatment refusal (Mystakidou et al., 2005; O'Mahonyet al., 2005), desire for hastened death (Mystakidou et al., 2005; O'Mahonyet al., 2005), frequent hospital admission (Wagner-Johnston et al., 2010) and significantly worse survival (Chow et al., 2016)

In most studies, the assessment of pain management quality is limited to the point prevalence and intensity of pain, which is insufficient. It is more meaningful to associate the data with pain treatment adequacy, patients' satisfaction with pain treatment, patients' quality of life, and the potential factors of severe or inadequate pain treatment.

Literature showed that approximately 40% of cancer patients potentially receive inadequate pain treatment (Roberto et al., 2022). Similar to prevalence of severe pain, Asian studies generally recorded higher rate of undertreatment compared to the studies from European countries (Roberto et al., 2022). In Malaysia, there is still lack of data on the adequacy of pain treatment among cancer patients (Mejin et al., 2019). Several studies have shown the negative implications of inadequate treatment, including decreased effectiveness of treatment, physical function interference, compromised emotional well-being, reduced social connections, and unnecessary use of healthcare resources (Gibson & McConigley, 2016; Potter et al., 2003).

Literature has shown that increased pain intensity (Deng et al., 2012) and inadequate pain treatment (Shen et al., 2017) in cancer patients are often associated with functional impairment and impaired quality of life. Considering the multidimensional nature of pain, ineffective pain management has detrimental impact on various aspects of life, including physical, mental, social, and spiritual well-being (Deng et al., 2012; Matsumura et al., 2021; Mikan et al., 2016; Shen et al., 2017). However, there were reports of inadequate attention has been given to the quality of life among the cancer patients (Breivik et al., 2009).

Patients' experience is one of the key determinants of successful pain management, with studies indicating that satisfaction level is associated with treatment adherence (Baker et al., 2013; Hirsh et al., 2005), pain severity (Lim et al., 2015; Tang et al., 2010) and adequacy of pain treatment (Ho et al., 2018; Lim et al., 2015; Shen et al., 2017). However, patients' satisfaction is not widely studied in cancer patients, particularly in the palliative care setting. In literature, the evaluation of patients' satisfaction with pain treatment was typically limited to the overall experience (Baker et al., 2016; Beck et al., 2010; Tang et al., 2010; Thinh et al., 2018). It would be useful to assess satisfaction in broader aspects, which may include effectiveness of medication in relieving pain, convenience in managing medication and experience of having adverse effect, in order to get more insights on the improvement of patients' experience.

Predictive factors of high level of pain severity and inadequate pain treatment have been studied but the findings were inconsistent across the studies (Deandrea et al., 2008; Greco et al., 2014; Issac et al. 2012; Knudsen et al., 2012; Stuver et al., 2012). The divergent results were probably due to the differences in study settings, methodologies, target populations, clinical characteristics and many other factors. In addition to this, findings from some studies may not be relevant or applicable to our population, particularly those conducted in developed countries with different socio-cultural backgrounds, geographic regions and healthcare settings.

Findings from most of the studies on cancer pain are more representative of the population with all cancer stages than those with advanced or terminal cancer. Despite of the increasing attention on the palliative care for the cancer patients with advanced cancer, there is relatively less published literature focusing on this population locally or globally, as it is challenging for researchers to collect self-reported data from this group of vulnerable patients with limited life expectancy. More studies are needed to better define the problems of cancer pain in these patients, to identify the treatment gap and to explore potential area for improvement in current practices.

1.3 Objectives of the Study

1.3.1 General Objective

To determine the prevalence and factors associated with severe pain and inadequate pain treatment, satisfaction with pain treatment and quality of life among cancer patients receiving palliative care.

1.3.2 Specific Objectives

- To determine the prevalence of severe cancer pain and inadequate pain treatment among cancer patients receiving palliative care.
- To assess the satisfaction with the pain treatment in cancer patients receiving palliative care.
- To assess the quality of life of cancer patients receiving palliative care.

- To identify factors associated with severe cancer pain and inadequate pain treatment among cancer patients receiving palliative care.

1.4 Significance of Study

The issue of cancer pain and its treatment among cancer patients particularly those in advanced, terminal or metastatic stage is poorly explored in the Malaysian context. Few previous studies have attempted to evaluate pain management among cancer patients who received palliative care in Malaysia, however, findings were generally confined to pain prevalence, severity of pain and adequacy of pain management (Mansor et al., 2008; Mejin et al., 2019). The present study explores on the various aspects of pain management, such as identifying subgroup with severe pain, factors associated with severe pain, adequacy of pain treatment, factors associated with inadequate pain treatment, satisfaction with the pain treatment and quality of life. Outcome from the present study can be considered as baseline for the future studies to further explore the above issues in our country, and the findings are also useful for us to recognize the unmet needs and areas of improvement.

1.5 Chapter Outline

Chapter 1 – This chapter provides an overview on the pain management in cancer patients including background of the issue, statement of problem, objectives of the research and the significance of conducting this study.

Chapter 2 – In this chapter, review of literature related to the study objectives is summarized. It provides current prevalence status and the associated factors of severe pain and inadequate pain treatment, as well as the patient-reported outcome including satisfaction and quality of life in patients with advanced cancer. The beginning of this chapter is a brief review of cancer pain, burden of cancer pain in advanced cancer patients and cancer pain with different intensity. This is followed by the discussion on the prevalence of severe cancer pain and adequacy of pain treatment based on Pain Management Index, in both worldwide and local setting. This chapter also provides summary of studies on the potential factors affecting severity of cancer pain and adequacy of pain treatment, satisfaction with pain treatment, and quality of life of cancer patients.

Chapter 3 – In this chapter, the description and justification of methodology are presented. The sections of this chapter include design of the research, study setting, duration of study, target population, sample size, sampling technique, eligibility criteria, ethical approval, instruments as well as the procedures of patient screening and recruitment. The final section is the discussion on the statistical tests used in analysis and interpretation of data.

Chapter 4 – The findings of the study are reported in this chapter. The statistical analysis of the prevalence and factors associated with severe cancer pain and adequacy of pain treatment, satisfaction level, and quality of life of the study population are presented in tables.

Chapter 5 – This chapter presents a detailed discussion of the results and the significance or importance of the findings. The similarities and differences of the findings in comparison with other studies in literature are also discussed.

Chapter 6 – This chapter serves as a concluding summary of the study findings. Additionally, strengths and limitations of the study are also included. Lastly, the implications on the practice in local setting and recommendations for future research are discussed in this chapter.

CHAPTER 2

LITERATURE REVIEW

2.1 Cancer pain

Pain is well-defined by The International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (Raja et al., 2020, p. 1976). The perception of pain is subjective with a broad range of inter-individual difference (Fillingim, 2017; Mogil, 2021). Traditionally, pain had been studied from the unidimensional perspective, but there has been increasing evidence showing that it is a multi-dimensional phenomenon (Fillingim et al., 2014; Kent et al., 2017; van Boekel et al., 2017). According to the concept of “total pain” suggested by Dame Cicely Saunders, pain is multidimensional and is characterized by a complex interplay of physical, social, psychological, and spiritual aspects (Mehta & Chan, 2008).

In the literature, cancer pain is not clearly or consistently defined (Bennett et al., 2019). However, the concept of multidimensional or multifaceted pain is widely acknowledged in the management of cancer pain (Ahles & Martin, 1992; Liu et al., 2017; Wool & Mor, 2005). By recognizing the multidimensional nature of cancer pain, it is important to adopt a more comprehensive approach in pain assessment and to tailor treatment by taking into account various interacting dimensions, in order to achieve a more holistic and personalized approach to cancer pain management (Liu et al., 2017).

In cancer patients, pain generally includes a wide range of pain conditions with different underlying causes, characteristics and mechanisms related to cancer (Caraceni

& Shkodra, 2019; Charak et al., 2021; WHO, 2018). As illustrated in Figure 2.1, several approaches have been used to categorize cancer pain according to etiology, pathophysiology and clinical characteristics (Bennett et al., 2019; Caraceni & Shkodra, 2019; Fainsinger et al., 2008; Hjermstad et al., 2009; Hwang et al., 2002). Cancer pain can be broadly categorized as acute or chronic, however, it is sometimes difficult to differentiate cancer pain between acute and chronic due to the progressive destruction of the cancer-related tissue (Bennett et al., 2019; Caraceni & Weinstein, 2001). Cancer pain can be due to cancer itself, metastasis or treatment of cancer (Bennett et al., 2019). For temporal presentation of cancer pain, it can generally be described as background pain or breakthrough pain (Bennett et al., 2019; Knudsen et al., 2009). With regard to the mechanism or pathophysiology of cancer pain, categories that commonly used in literature including nociceptive which can be sub-categorized as somatic and visceral, neuropathic, mixed, psychogenic as well as idiopathic (Knudsen et al., 2009). Cancer pain can be categorized according to intensity or severity as mild, moderate and severe (Caraceni & Shkodra, 2019; Charak et al., 2021), this will be further discussed in section 2.2. Cancer patients often have pain from more than one site or source particularly in patients with advanced cancer where the pain is related to metastasis (Caraceni & Shkodra, 2019).

In an international survey to explore the cancer pain characteristics among 1095 cancer patients from 24 countries, Caraceni et al. (1999) revealed 92.5% of them experienced pain due to the cancer itself, 20.8% caused by the cancer treatment and 2.3% claimed the pain was neither related to cancer nor the treatment of cancer. The authors also reported that approximately a quarter of the patients had pain from more than one source and two-thirds of the patients experienced breakthrough pain. The same study also showed the pain pathophysiology varied greatly among the patients, with 71.6% had nociceptive somatic pain, 34.7% nociceptive visceral pain and 39.7% neuropathic pain. In another more recent survey on 1051 patients with advanced cancer from European countries, Canada and Australia, 79.7% of them had nociceptive pain, 16.9% had neuropathic pain and 60.9% had breakthrough pain, these results were consistent with findings from the aforementioned study (Nekolaichuk et al., 2013).

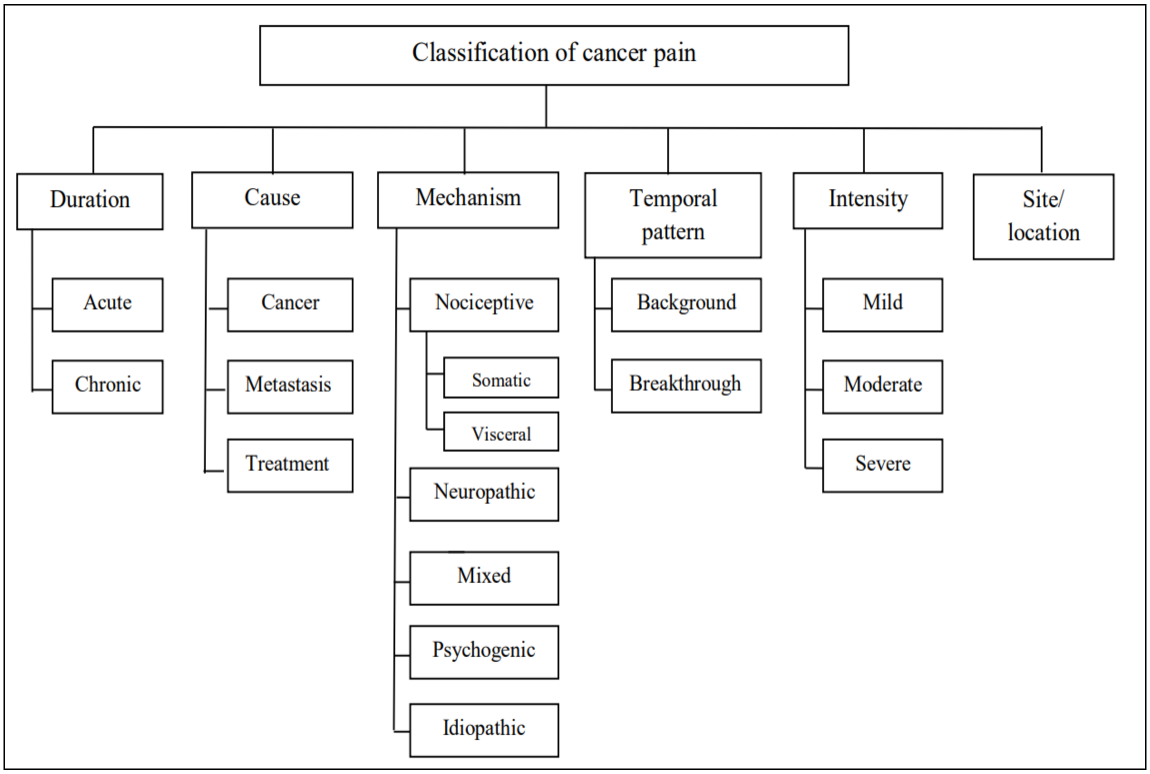

Figure 2.1 Classification of cancer pain

Several multidimensional assessment tools (Cleeland & Ryan, 1994; Melzack, 1987) and guidelines (Fallon et al., 2018; NCCN, 2002) are available in the cancer pain assessment, however, there is still no universally accepted tool or concensus on which domains to be included (Hjermstad et al., 2009; Stewart, 2014). Ideally, a pain assessment tool should have important features such as short, precise, multifaceted and specific for the target population (Hjermstad et al., 2009). Several important domains or approaches have been identified by researchers or experts to be included in the pain assessment. Knudsen et al. (2012) suggested pain characteristics, pathological mechanism, as well as patient factors such as psychological and social factors, should be included. For cancer patients receiving palliative care, a panel of experts from various countries recommended pain intensity, temporal characteristics, treatment, aggravating or relieving factors, location, and impact on quality of life, as the important aspects in pain assessment (Hølen et al., 2006). In addition to comprehensive assessment at initial presentation, Hui & Bruera (2014) commented successful pain management requires longitudinal assessment over the time with appropriate dose titration and management of adverse effects.

2.1.1 Cancer pain in patients with advanced cancer

The advanced stage of cancer is often associated with more complex clinical presentation, which poses greater challenges for pain management (Mercadante, 2019). Review of literature consistently showed that cancer patients particularly at advanced stage experienced high symptom burden. There are several factors that contribute to the high symptom burden in cancer patients, including cancer itself, the side effects of treatment, functional impairment, psychological distress, and the presence of comorbidities (He et al. 2022; Lage et al., 2020). A systematic review of 46 studies identified 37 symptoms among 26,223 patients with advanced cancer, with pain being one of the most predominant symptoms, occurring in more than half of the patients, and it remained as the frequently reported symptom in the last one to two weeks of life

(Teunissen et al. 2007). In a more recent systematic review, Gilbertson-White et al. (2011) revealed that 56 symptoms were reported in palliative care patients with advanced cancer, and pain was identified as one of the symptoms across all the 22 studies. Findings from several studies also suggested that pain tended to cluster with other symptoms in cancer patients (Chen & Tseng, 2006; Fan et al., 2007; Özalp et al., 2017). In a review of 32 studies on symptom clusters in patients with advanced cancer, Dong et al. (2014) revealed that pain tended to co-exist with symptoms of fatigue, dyspnea and drowsiness in 45% of the studies, however, the cluster did not show consistency over the time.

A consistent finding from literature is the prevalence or incidence rate of pain is higher in the patients with more advanced disease. Hyun et al. (2003) reported patients with metastatic cancers were more likely to experience pain than those without metastasis, and the prevalence of moderate-severe pain increased progressively with higher stage of cancer ($p < 0.0001$). In a large study of cancer patients in Netherlands, van den Beuken-van Everdingen et al. (2007b) found that advanced stage of cancer was one of the positive predictive factors of the higher prevalence of pain. A systematic review of 122 studies published from 2005 to 2014 summarized that two-thirds (66.4%) of patients with advanced, metastatic or end stage cancer had pain, it was significantly higher compared to 55% in subgroup of cancer patients receiving anticancer treatment and 39.3% in patients who had completed curative therapy ($p = 0.032$, $p < 0.001$ respectively). The same study also revealed that more than half (51.9%) of these terminally ill cancer patients scored their pain intensity at level of moderate to severe, in contrast to 32.4% of the patients receiving anticancer treatment and 27.6% of the patients who had completed curative treatment ($p = 0.005$, $p = 0.002$, respectively) (van den Beuken-van Everdingen et al., 2016). In a multicentre study of patients with advanced cancer, results from the secondary analysis showed patients with moderate and severe pain took significantly longer duration to achieve good pain control ($p < 0.0001$), consumed higher doses of opioid ($p < 0.0001$), and required more adjuvant analgesics ($p = 0.015$) (Fainsinger et al., 2009).

2.1.2 Cancer pain and palliative care

According to the WHO (2002), palliative care is defined as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, whether physical, psychosocial, and spiritual" (p.84).

Palliative care is applicable to individuals who experience serious health related suffering due to various progressive life threatening conditions such as cancers, chronic organ failures, neurodegenerative disorders, chronic life-threatening infections, incurable genetic diseases and elderly individuals with multiple co-morbidities and frailty (MOH, 2019). In the context of cancer, palliative care is not limited to end-of-life care or solely intended for patients at advanced or terminal cancer with significant symptom burden, such as pain. It is also offered to individuals at any stage of the disease suffering from physical symptoms, psychosocial challenges or spiritual distress, even if they are undergoing active anticancer treatment (Academy of Medicine Malaysia [AMM], 2015; MOH, 2010b). In the provision of palliative care to cancer patients, cancer-related pain is widely recognized as a highly prevalent and challenging symptom (Henson et al., 2020; Yoong & Poon, 2018).

Literature consistently demonstrates the effectiveness of palliative care in controlling cancer pain in cancer patients. In a meta-analysis of 18 studies, Zhao et al. (2019) reported substantial pain improvements among cancer patients in China who received palliative care (Standardized Mean Difference = 1.475, $p < 0.001$; 95% CI = 1.071–1.878). In a study of cancer patients admitted to the hospital for pain control, it was observed that those who received additional care from the palliative care team exhibited a statistically significant greater improvement compared to the control group who received traditional care ($p < 0.001$) (Jack et al., 2006). In a qualitative study conducted by Brooks et al. (2020) to explore the experiences and perceptions of cancer patients and oncologists regarding palliative care, patients reported that palliative care improved pain management and helped to reduce the misconception associated with pain treatment whereas oncologists provided feedback indicating that collaborating with palliative care teams facilitated the management of complex pain cases.

2.2 Pain intensity in cancer patients

Pain intensity or severity in cancer patients has been well studied. Pain intensity is generally regarded as an important pain characteristic and gold standard in pain reporting or assessment, which facilitates clinical decision making in the treatment selection (Caraceni & Shkodra, 2019). Management of cancer pain in numerous consensus and guidelines such as WHO Analgesic Ladder (WHO, 1986, 2018), National Comprehensive Cancer Network guideline (2022), European Society for Medical Oncology (ESMO) guidelines (Fallon et al., 2018) are based on the classification of pain intensity as mild, moderate, or severe. In several expert surveys and literature reviews, pain intensity has often been ranked as one of the most important dimensions to be included in multidimensional assessment of cancer pain (Hjermstad et al., 2008, Hølen et al., 2006).

The severity of pain was reported to substantially affect the quality of life and influence treatment decisions (Chow et al., 2006). Te Boveldt et al. (2013) reported that pain interference on daily activities increased with aggravation in pain severity. In the patients with mild, moderate and severe pain, median scores of pain interference on daily activities such as mood, ambulatoty ability, work, social interactions, sleep, and life enjoyment were 1.1, 3.1 and 4.9 respectively ($p < 0.0001$) (Te Boveldt et al., 2013). Vallerand et al. (2007) also reported that pain level was positively correlated with distress level ($r = 0.9$) and interference on functional status ($r = 0.83$). Results from a recent study showed worst pain score was significantly correlated with global QoL, physical and emotional functions ($\rho = - 0.36$, $p = 0.031$; $\rho = - 0.33$, $p = 0.043$; $\rho = - 0.46$, $p = 0.006$, respectively) (Matsumura et al., 2021).

Apart from the positive association between pain severity and duration to achieve pain control, opioids dose and use of adjuvant analgesics (Fainsinger et al., 2009), literature also showed that patients with higher baseline pain intensity were at higher risk to have marked fluctuations in pain intensity. Zhu and colleagues (2012) reported the adjusted odd ratios of pain variability for mild, moderate and severe pain were 0.80, 1.77 and 7.70 respectively. The same authors also revealed that high pain intensity combined with remarkable fluctuations predicted poor overall survival. In the study, patients with wide pain variability and aggravation of pain showed worst 1-year survival probabilities (39.1%) compared to those with less fluctuations (59.2%) and with marked pain variability but improving pain intensity (79.5%) (Zhu et al., 2012).

In a small study, Mercadante et al. (2013a) observed that patients who required medication for breakthrough pain were likely to have pain score of 7 and above, and patients who were satisfied after taking the breakthrough dose were likely to have a pain score of 4 or less. In another study, Valeberg et al. (2008) suggested to use average pain rating above 4 in screening of cancer outpatients presented with clinically significant pain, based on the findings of pain score greater than 4 was highly associated with breakthrough pain ($p = 0.03$), and was generally associated with lower scores in various aspects of life such as physical, role, cognitive, and global health function.

Three frequently used pain intensity assessment tools in research and clinical practice are Numerical Rating Scale (NRS), Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS) (Caraceni et al., 2005; Hjermstad et al., 2011; Williamson & Hoggart, 2005) with established reliability, validity and applicability (Jensen, 2003; Williamson & Hoggart, 2005). However, it is not easy to use VAS in patients who are frail or visually impaired, and VRS is considered a relatively crude measure with the mere classification of mild, moderate and severe pain (Woo et al., 2015). In clinical trials, the NRS exhibited higher reliability than the VAS, especially in patients with lower literacy (Ferraz et al. 1990). In a study of advanced cancer patients, Brunelli et al. (2010) reported NRS was considered more useful in distinguishing background pain and worst pain intensity, and reproducible in measurement of the exacerbations in pain. Paice and Cohen (1997) reported NRS was statistically significantly correlated to VAS, supporting the validity of NRS administered verbally to cancer patients. Hjermstad et al. (2011) suggested that important aspects such as administration method, time allocation, cut-off points and their clinical significance, use of outcome measures, and scale related information to be considered in the selection of scales.

As discussed earlier in this section, defining pain based on its severity is important not only to provide a brief guide in the initiation and selection of pain treatment, but also to describe study outcomes, such as treatment effectiveness, changes in functional status and quality of life, in a more clinical meaningful way (Anderson, 2005; Woo et al., 2015). However, the cut-off points used in defining the pain intensity according to mild, moderate and severe show some variations. Cleeland et al. (1994) defined pain score of 1 to 3 as mild, 4 to 7 as moderate and 8 to 10 as severe. Serlin et al. (1995) later determined pain rating of 1 to 4 corresponding to mild, 5 to 6 to moderate, and 7 to 10 to severe, based on the statistical analysis of functional interference caused by pain in cancer patients. This definition was later supported by Li et al. (2007) in a study of cancer patients with bone metastases. Paul et al. (2005) also confirmed the cut-off point between mild and moderate of cancer pain was at 4 as reported by Serlin et al. (1995). In a study on cancer patients with bone metastases, Chow et al. (2006) reported 60% of patients categorized pain as mild rated it at score of 3 or 4, 63% categorized pain as moderate rated it at 5, 6 or 7 and 80% categorized pain as severe rated it at 8 or 10. In a systematic review, Woo et al. (2015) summarized mild-moderate pain cut-off points ranged from 1 to 4, with 4 being highly recommended, whereas for moderate to severe pain, cut-off points ranged from 4 to 7 with 6 was the optimal one.

2.3 Prevalence of severe pain in cancer patients

In a systematic review on the studies published from 2005 to 2014, the prevalence of severe pain varied greatly according to different subgroups of cancer patients (van den Beuken-van Everdingen et al., 2016). About 8% to 43.7% of patients in the subgroup of all stages of cancer were reported to have severe pain. In the patients who were receiving anticancer treatment, 3.6% to 39.7% of them had severe pain. Prevalence of severe pain was lowest in the patients who had completed curative treatment, from as low as 0.5% to 13%. On the other side, the prevalence of severe pain was highest in patients with advanced, metastatic, or terminal cancer, ranging from 3.1% to as high as 78.2%. In this subgroup, studies from Asian countries generally showed higher rate of severe pain than those from the countries in North America and Europe (30-78.5%, 5.2-39.6% and 17-35.2%, respectively). However, the authors did point out a methodological limitation, noting that not all studies used the same criteria to define mild, moderate, or severe pain (van den Beuken-van Everdingen et al., 2016).

In Asian region, the prevalence data on severe pain in cancer patients mostly derived from the studies conducted in South Korea, Japan and Taiwan. Findings from two nationwide studies in Korea showed that prevalence of severe pain (pain score ≥7) in cancer patients treated in both out-patient and in-patient setting was 15.3% and 10.6%, in 2001 and 2006 respectively (Hong et al., 2011). According to a nationwide study in Taiwan, Shen et al. (2017) reported the percentage of severe pain (pain score ≥8) among outpatients with cancer was 15.3%. In a study of Japanese cancer patients, Mikan et al. (2016) reported the prevalence rates of severe pain (pain score ≥7) in the cancer patients treated in the setting of outpatient, inpatient and palliative care unit, were 5%, 13% and 24% respectively. All these studies exhibited variations in the definition of severe pain and differences in study settings, which complicate the interpretation of the findings.

By narrowing the focus to studies conducted in Asian region with outpatient palliative care setting and using the same definition of severe pain as the present study (i.e., pain scores of 7 and above), a limited number of studies showed that the prevalence of severe pain in this population was not considered highly satisfactory. In a nationwide survey in Japan, Yamagishi et al. (2012) revealed 7.7% of all cancer patients in the study had severe pain based on worst pain ratings, this equated to about 12.8% of the patients with pain described their pain as severe. In a study published 2 years later, Morita et al. (2014) reported 7.6% of the study population with metastatic or advanced cancer had severe pain, in other words, 12.9% of the patients with pain experienced severe pain.

In Malaysia, data on the prevalence of severe pain among cancer patients receiving palliative care is limited to in-patient setting only. Mejin et al. (2019) reported 58.5% of cancer patients experienced severe pain upon admission to palliative care unit based on worst pain score of 7 and above, and 5% of them still had severe pain upon discharge. Taking into account the dynamic nature of pain, the authors highlighted the importance of ongoing monitoring and follow-up of cancer patients in palliative care to effectively address and manage pain (Mejin et al. 2019).

2.4 Prevalence of inadequate pain treatment in cancer patients

There are extensive literatures exploring the quality and appropriateness of pain treatment in cancer patients using Pain Management Index (PMI) introduced by Cleeland et al. (1994).

In a recent systematic review of 20 studies published from 2014 to 2020, Roberto et al. (2022) reported that the weighted mean percentage of negative PMI, which represents the prevalence of inadequate pain treatment among cancer patients, was 40%, with a range of 6% to 67%. The weighted mean percentage of negative PMI was calculated based on the sample sizes of the individual studies to achieve a more accurate estimation of the overall negative PMI percentage (Roberto et al., 2022). Two earlier systematic reviews published in 2008 and 2014 showed the rate of undertreatment were

43% and 32% respectively (Deandre et al., 2008; Greco et al., 2014). Even though it showed the trend of improvement between 2008 and 2014, the findings from the most recent review showed an upward trend in the rate undertreatment (Roberto et al., 2022). In the same review, the analysis of all the publications from 1994 to 2020 showed the decline rate of undertreatment was approximately 0.8 point yearly, after adjusting other confounding factors such as study setting, sample size, age of study population, quality score of studies, and economic status of the country (Roberto et al., 2022). The changes on the adequacy of pain treatment over the years were summarized in the Table 2.1 below.

Table 2.1 Prevelance of undertreatment based on PMI and the change of the prevalence according to years of publication

Year of publications	Number of studies	Weighted mean of negative PMI (%)	Range of negative PMI (%)	Change (%)
1994- 2000	12	47	27-79	
2001- 2007	14	42	8-82	-11
2008- 2013	20	32	4-68	-32
2014- 2020	20	40	6-67	-14

Adapted from "Living systematic review to assess the analgesic undertreatment in cancer patients" by Robertoet al. (2022), *Pain practice : the official journal of World Institute of Pain*, 22(4), p487-496

In general, Asian studies recorded higher rate of undertreatment in comparison with the studies from European countries, with the weighted mean percentage of negative PMI 59% vs 40%, 42% vs 29% and 41% vs 35% for the years of 1994-2007, 2008-2013 and 2014-2000, respectively (Roberto et al., 2022).

It is worth noting that, patients in the group with higher rate of metastasis were more likely to receive adequate pain treatment than the group with lower rate of metastasis, over the years of 1994 to 2000 (Roberto et al., 2022). The comparison of weighted mean percentage of negative PMI among these 2 groups were 31% vs 58%, 19% vs 38% and 30% vs 45%, for the years of 1994-2007, 2008-2013 and 2014-2000, respectively (Roberto et al., 2022).

In Malaysia, data on the adequacy of pain treatment among cancer patients is still limited to the in-patient setting. A recently published study showed that 69.9% of cancer patients were potentially undertreated for cancer pain upon admission to palliative care unit, however, all of them were adequately treated upon discharge (Mejin et al., 2019). These findings may not be directly applicable to cancer patients receiving palliative treatment in the outpatient setting.

It is known that measurement of adequacy of pain control based on PMI can only capture pain intensity relative to class of analgesics used. Limitations of using PMI were recognized and acknowledged in literature. It does not take into consideration of other important pharmacological factors such as dosage, schedule, route of administration, titration, patients' compliance, and use of adjuvant pain medication (Deandrea et al., 2008; Foley, 2011; Okuyama et al., 2004; Roberto et al., 2022; Sakakibara et al., 2018). In addition to these, Takahashi et al. (2017) commented difference in definition of denominators and cut-off points used in calculation of the PMI may result in some variations in the percentage of patients with negative PMI.

2.5 Satisfaction with pain treatment in cancer patients

The concept of incorporating patient satisfaction in pain management was introduced in the 1990s. The Quality Assurance Committee of the American Pain Society (APS) proposed assessment of patient satisfaction as part of the standards in pain management (Bond et al., 1991). The standards were revised in 1995 with inclusion of additional items related to patients' rating of satisfaction (Max et al., 1995). In addition to this, the Initiative in Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) recommended patient-rated satisfaction as one of six core domains that should be considered in clinical trials of chronic pain treatment (Turk et al., 2003, 2006).

Literature showed that patients' satisfaction with pain treatment directly influences their adherence to pain treatment (Hirsh et al., 2005; Baker et al., 2013). However, satisfaction is not widely studied in cancer patients, particularly those patients receiving palliative care.

There were some studies on the potential factors affecting satisfaction among cancer patients, but the findings were not consistent. In a survey of 1,370 terminally ill cancer patients in Taiwan, Tang et al. (2010) found that factors such as older age, female gender, absence of co-morbidity, pain relief, low pain intensity, right amount of pain medication, short waiting time for pain medication, consistent information and understandable explanation on the pain treatment were significantly predictive of greater satisfaction with pain treatment. ($p = 0.002$, $p < 0.001$, $p = 0.009$, $p = 0.04$, $p = 0.03$, $p < 0.001$ and $p = 0.002$, $p = 0.003$, $p = 0.01$ and $p < 0.001$, respectively). Similarly, Baker et al. (2016) found that older patients had higher tendency to feel satisfied with their pain treatment compared to those in middle-aged group. Middle-aged patients generally had lower treatment satisfaction with greater pain severity, whereas for older patients, satisfaction level remained consistent despite of higher pain severity (Baker et al., 2016). In contrast, Kim et al. (2013) reported the overall satisfaction rate on pain control perceived by the 7507 cancer patients in Korea was 78.7%, and it was not significantly