Mood Disorders in Cancer Patients With or Without Arthritis: Incidence and Impact on Health Care Utilization

by Umme Saika Kabir

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

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List of Abbreviations

CI – Confidence interval

DAD – Discharge Abstract Database

ED- Emergency Department

HCU- Health Care Utilization

HR – Hazard Ratio

ICES – Institute for Clinical Evaluative Sciences

IDAVE – ICES Data & Analytic Virtual Environment

MDD – Major Depressive Disorder

MMB- Multimorbidity

NACRS – National Ambulatory Care Reporting System

OA- Osteoarthritis

OCR – Ontario Cancer Registry

OHIP – Ontario Health Insurance Plan

ON-Marg – Ontario Marginalization Index

RA- Rheumatoid Arthritis

RPDB – Registered Persons Database

Abstract

Objectives: This thesis is aimed to detect the incidence of mood disorders in cancer patients, and to assess the role of arthritis and multimorbidity in the development of mood disorders. The thesis will also describe the impact of arthritis and mood disorders on the health care utilization of cancer patients accounting for the role of other comorbidities.

Methods: The thesis is a population-based study with linked administrative health databases, available from the Institute for Clinical Evaluative Sciences, and included all adult patients diagnosed with cancer in Ontario between 2003 and 2013. The study used a retrospective cohort design. Univariate and bivariate analyses were used to describe the incidence of mood disorders, level of multimorbidity, and characteristics of patients with cancer. Survival analysis was used to evaluate the adjusted impact of arthritis and other variables on the occurrence and time to the development of mood disorders. Negative binomial regression was performed to assess the adjusted effect of arthritis and mood disorders on health service utilization by cancer patients.

Results: The cumulative crude incidence of mood disorders over the study period in cancer patients in Ontario was 16.9 (95% CI 16.6-17.3)/1,000 population. Arthritis was not associated with an increased risk of developing mood disorders in crude and adjusted analysis; however, multimorbidity significantly increased the risk of mood disorders. Mood disorders and arthritis increased health care utilization in cancer patients. The average hospitalizations per person-year in patients with mood disorders diagnosed before (0.73± 1.06) and after (1.09 ± 1.33) cancer was higher than patients without mood disorders (0.57 ± 0.92). Similarly, average ED visits per person-year were also higher when mood disorders were diagnosed before (1.03 ± 1.68) or after (1.20 ±

2.10) cancer compared to the patients without mood disorders. Arthritis increased only ED visits while decreasing hospitalization. When mood disorders and arthritis were both present in patients with cancer and diagnosed after cancer there was a 28% (95% CI = 20-37%) higher risk of hospitalization and a 60% (95% CI = 50-69%) increased risk of ED visits compared to those without any of these conditions.

Conclusion: The study provided evidence on the risk of developing mood disorders in cancer patients with multiple chronic conditions. Multimorbidity is an important risk factor for developing mood disorders and the number of chronic conditions rather than a specific condition like arthritis increases the likelihood of developing mood disorders. The study showed the importance of addressing multimorbidity to improve the mental health outcomes in cancer patients. The findings of the study also described the impact of arthritis and mood disorders on the health service utilization of cancer patients. Mood disorders increased health services use more than arthritis. Early identification of psychological and other chronic conditions may decrease hospital admissions and ED visits in cancer patients reducing the burden and cost of the health care system.

Overview of Thesis Content

The thesis is organized into seven chapters. Chapter 1 provides a general introduction to the topic and includes a discussion of multimorbidity in cancer patients, arthritis, mood disorders, and health care utilization. The second chapter is the literature review, synthesizing detailed knowledge about the study topics and the possible research gaps. The third chapter is the overview of the thesis methodology including the approach to the study, objectives and hypothesis, conceptual frameworks, and general methods. Specifically, the fourth and fifth chapters address the main objectives in the form of manuscripts for publications. The fourth chapter addresses the first objective of the thesis, i.e. the impact of arthritis on the development of mood disorders in cancer patients and whether this association varies by the level of multimorbidity. The fifth chapter addresses the other objective, i.e. the impact of arthritis and mood disorders on the health care utilization of cancer patients while considering the number of other comorbid conditions. The sixth chapter is comprised of the general study findings with a brief discussion of the epidemiological aspects with the strengths and limitations of the thesis. The seventh and final chapter describes the implications of the study findings and the direction for future research.

Chapter 1: Introduction

Non-communicable diseases are becoming the greatest group of health concerns in the world and responsible for the majority of global death (World Health Organization, 2018). This includes cancer, one of the leading causes of death internationally, and particularly in developed countries (Bray et al., 2018). One in two Canadians is at risk of developing cancer in his or her lifetime (Canadian Cancer Society, 2017), and one in every four Canadians is expected to die from the disease (Canadian Cancer Society, 2018). In Ontario, the number of newly diagnosed malignant cancers in 2018 was 90,483; this equates to an age-standardized incidence of 571.1 cases per 100,000 people (Cancer Care Ontario, 2018). The survival of cancer patients has been increased markedly over the decades in Canada. Ellison (2018) reported that the median increase in 5-year net cancer survival was 6.9-8.6% between the ages of 15 to 74 years within the last twenty years (Ellison, 2018).

People with cancer are also often faced with the co-occurrence of multiple chronic conditions, or multimorbidity (MMB). In Canada, among the general population, 25% or more individuals aged above 40 years have MMB, and MMB is even higher in the elderly population (Feely et al., 2017; Koné Pefoyo et al., 2015). In Ontario, over 75% of cancer patients have at least one additional chronic condition (Feely et al., 2017; Koné Pefoyo et al., 2015). MMB is positively associated with mortality in older adults, and the risk of death increases with the number of chronic conditions (Nunes et al., 2016). MMB in cancer patients results in reduced survival, lower quality of life, complexity in treatment, poorer outcomes, and cancer patients with MMB often represent high-cost users of the health care system (Lee et al., 2011; Perruccio et al., 2007; Sarfati et al., 2016; Søgaard et al., 2013; St John et al., 2014).

Clustering of chronic conditions with cancer may be due to common risk factors with cancer, such as old age, smoking, alcohol, poor diet, lack of physical activities, and obesity (Extermann,

2007; Sarfati et al., 2016). Cancer often occurs in combination with musculoskeletal diseases (including arthritis), cardiovascular diseases, metabolic diseases (such as hypertension, hyperlipidemia, diabetes), and gastrointestinal conditions; mood disorders (such as depression) are particularly prevalent in cancer patients (Kenzik et al., 2016; Koné Pefoyo et al., 2015; Massie, 2004; Roy et al., 2018). Studies have reported the prevalence of depression among cancer patients in the range of 20-40%, and at least 15% of cancer survivors have a diagnosis of major depressive disorder (MDD) (Lima et al., 2016; Pitman et al., 2018). Polsky et al. (2005) found that patients newly diagnosed with cancer were approximately four times more likely to develop depressive symptoms compared to the persons having no cancer (Polsky et al., 2005). Another study has reported that among cancer patients seeking mental outpatient services, at least 18% have mood disorders (Anuk et al., 2019).

The prevalence of mood disorders among cancer patients increases with multimorbidity; inflammatory conditions characterized by pain like arthritis, cancer, fibromyalgia, and heart diseases show associations with mood disorders (Anuk et al., 2019; S. B. Patten et al., 2018; Scott B. Patten, 2005). For example, arthritis has been positively linked with mood disorders including depression in several research studies (Choy & Calabrese, 2018; Nicassio, 2010; Sturgeon et al., 2016). A meta-analysis by Sturgeon et al. (2016) has reported that the prevalence of MDD in patients with rheumatoid arthritis is 16.8% whereas the lifetime prevalence of MDD among the US general population is 7.1% (Sturgeon et al., 2016; National Institute of Mental Health, 2019). Cancer diagnosis, pathophysiology, and its treatment, including chemotherapy, are associated with the development of mood disorders especially depression (Anuk et al., 2019; Pitman et al., 2018; Smith, 2015). Depressive disorders cause physical distress, decreased quality of life, poor treatment compliance, thus, negatively impact cancer outcomes and complicates care management

(Colleoni et al., 2000; Fitzgerald et al., 2015; Kanani et al., 2016; M. Li et al., 2016; Pinquart & Duberstein, 2010). Moreover, patients diagnosed with cancer and depression are likely to have more hospital admissions, extended hospital stays, increased number of emergency and primary care visits (Mausbach & Irwin, 2017; R. Patel et al., 2018).

The occurrence of mood disorders in cancer patients has been addressed in the literature, while cancer and musculoskeletal conditions are proved to each be associated with mood disorders. However, the effects of arthritis on the development of mood disorders in cancer patients still remain unknown. This study will examine the impact of arthritis on the development of mood disorders in cancer patients. We will also test the hypothesis that the co-occurrence of arthritis and mood disorders increases health services use among cancer patients. We will evaluate the combined impact of arthritis and mood disorders on health care utilization among cancer patients in terms of hospital admissions and emergency (ED) visits. Although several studies have focused on health care utilization (HCU) in cancer patients, this proposed study is novel because we use a robust population-based design to determine the influence of MMB, particularly arthritis and mood disorders on cancer patients' HCU.

Chapter 2: Literature Review

The study is intended to describe the impact of arthritis on the development of mood disorders in cancer patients as well as how this cluster of comorbidities affects health service utilization. Therefore, the review of the literature will be related to the following key concepts relevant to the study; cancer, arthritis, multimorbidity, depression, and health care utilization. We conducted a literature search to understand the current body of knowledge regarding these topics. PubMed was searched in June 2019 and in May 2020 with specific keywords including comorbid*, "Comorbidity"[Mesh], "Multimorbidity"[Mesh], MDD [Mesh], Arthritis [Mesh] depress*, “Depressive Disorder"[Mesh], malignan*, cancer*, "Neoplasms"[Mesh], “Cancer AND mood disorders”, “Arthritis AND mood disorders”, “Cancer AND Hospitalization”, “Cancer AND Health care utilization” “Arthritis AND Health care utilization”, “ Mood disorders AND health care utilization.”

Articles focusing on the prevalence of mood disorders in cancer patients, the impact of mood disorders on cancer outcomes, including HCU, and treatment were selected for further review. We also included the papers describing multimorbidity (MMB) in cancer patients, including arthritis and its impact on the development of mood disorders as well as HCU. The literature review provided a detailed description of cancer and its burden, MMB in cancer patients, development of mood disorders in cancer patients, the role of arthritis on the development of mood disorders, sociodemographic factors, the biological mechanism of cancer, arthritis and mood disorders, and the impact of MMB especially arthritis and mood disorders on the utilization of health care services by cancer patients.

2.1 Cancer Burden and Risk Factors

“Cancer is a disease where abnormal cells divide without control and can invade nearby tissue. Cancer cells can also spread to other parts of the body through the blood and lymph systems”

(National Cancer Institute, n.d.). The incidence of cancer is increasing, and in 2018, there were 18.1 million new cancer cases diagnosed globally compared to 12.7 million in 2008 (Bray et al., 2018; Jemal et al., 2011). The World Health Organization ranked cancer as the second leading cause of death worldwide in 2018, with an estimated 9.6 million deaths attributed to cancer (World Health Organization, 2018). Cancer was previously known as the disease of high-income countries, although the prevalence is now rising in the low and middle-income countries due to aging populations and lifestyle factors (Bray et al., 2018; Torre et al., 2016).

In Canada, 225,800 newly diagnosed cancer cases are expected in 2020, of which 83,300 will die from the disease (Brenner et al., 2020). There are wide provincial differences in the incidence rate of cancer. Eastern Canada comprised of Atlantic Canada, Quebec, and Ontario has a higher incidence rate of cancer, while British Columbia continues to have the lowest incidence rate (Xie et al., 2015). Within the period 2013-17, the age-specific incidence rate (ASIR) of all cancers among males was 392 per 100,000 person-year in British Columbia, whereas, in Atlantic Canada, the ASIR was as high as 545 per 100,000 person-year in Prince Edward Island (Xie et al., 2015). Cancer is the leading cause of mortality and the seventh most costly illness in Canada (Canadian Cancer Society, 2017). According to a recent Canadian Cancer Society report, the 5-year net survival for all cancers combined is 63%, and slightly higher for females than males (Canadian Cancer Society, 2019). The highest cancer mortality in Ontario in 2018 is attributable to lung, colorectal, female breast, and pancreatic cancer (Cancer Care Ontario, 2018). The incidence rate and mortality rates are higher in males and people aged 60-79 (Cancer Care Ontario, 2018). It is predicted that the healthcare system in Canada will face challenges for the appropriate care management of cancer patients in the future (Canadian Cancer Society, 2017).

Cancer can occur in almost any site of the body, such as lung, brain, skin, gastrointestinal tract, breast, reproductive organs, kidney, blood, and so on (Bray et al., 2018; Xie et al., 2015). However, the most prevalent cancer sites vary substantially by age, sex, and sociodemographic characteristics (Bray et al., 2018). In Canada, in 2019, the most frequently occurring cancers among males irrespective of age are prostate, lung, colorectal, bladder, and lymphoma, whereas, the most prevalent cancers in females are breast, lung, colorectal, uterus, and thyroid (Canadian Cancer Society, 2019).

Cancer results from a complex interplay between genetic, environmental, and lifestyle factors (Wei et al., 2010; Wu et al., 2018). Heredity has been proven to play a role in breast, colon, and several childhood cancers (Frank, 2004; Tomasetti & Vogelstein, 2015). Other non-modifiable risk factors contributing to the development of cancer include age, male sex, family history, ethnicity, and hormones (Wu et al., 2018; Canadian Cancer Society, 2019). A study conducted in the Czech Republic describes that among the 80,000 newly diagnosed cancer patients each year, the majority are aged 55 years or older (Smetana Jr. et al., 2016). The authors hypothesize that aging causes irreversible cellular damage which increases the likelihood of developing cancer (Smetana Jr. et al., 2016). According to the Canadian Cancer Society, in the age group 20-59 years, females have a higher incidence of cancer, whereas, in all other age groups, males are predominantly affected (Canadian Cancer Society, 2017). There is also a racial variation of cancer prevalence in Canada; Caucasians have a higher prevalence of cancer (Lebrun, 2011).

Smoking is the most important modifiable risk factor for many cancers including lung, esophagus, throat, oral, colorectal, larynx, kidney, urinary bladder, liver, pancreas, stomach, breast, ovary, and cervix(Gapstur et al., 2018; Y.-S. Sun et al., 2017). Alcohol, lack of physical activity, obesity, and diets deficient in fruits and vegetables are other modifiable risk factors for

various cancers including breast, colorectal, prostate, and liver cancer (Gapstur et al., 2018; Key et al., 2004; A. Patel et al., 2018; Y.-S. Sun et al., 2017; Tan et al., 2018; Wei et al., 2010). Environmental exposures, for example, radiation, carcinogenic chemicals, sunlight, second-hand smoking, and certain infections like Human Papilloma Virus (HPV), Human Immuno Deficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Helicobactor pylori also represent risk factors for developing cancer (Gapstur et al., 2018; Wei et al., 2010; Canadian Cancer Society, 2017). Cancer risk factors vary according to sociodemographic characteristics. For example, in high-income countries smoking, obesity and alcohol are associated with the development of a majority of cancers, whereas, in low and middle-income countries associated factors are smoking, deficient diet, and sexually transmitted HPV infection (Danaei et al., 2005).

2.2 Multimorbidity (MMB) in Cancer Patients

Multimorbidity is the presence of multiple diseases in an individual, often defined as the co-occurrence of two or more diseases (Feely et al., 2017; Johnston et al., 2019; Koné Pefoyo et al., 2015). MMB is more common among the elderly, females, people from the lower-income quintiles, low educational attainment, and Indigenous populations (Kuwornu et al., 2014; Roberts et al., 2015; Skivington et al., 2015). In Canada, the prevalence of MMB is around 26%, reaching 66% for people above 65 years of age (Feely et al., 2017). The highest prevalence is observed for asthma, diabetes, hypertension, arthritis, and mood disorders (Lebenbaum et al., 2018; Roberts et al., 2015).

MMB is common among cancer patients and survivors. A cohort study based on population health administrative data in Ontario reports that around 75% of cancer patients have at least two conditions and 25% have three or more conditions besides cancer (Koné Pefoyo et al., 2015). Older cancer patients are more likely to have comorbid conditions as age is a common risk factor for

cancer and MMB (Corbett & Bridges, 2019). Cancers associated with the highest comorbidities include prostate, breast, colorectal, and cervical cancer, which may be explained by the longer survival rate for these cancer types (Salako et al., 2018). A population-based cross-sectional study conducted in Australia reported an increased prevalence of mental/behavioral problems, musculoskeletal and circulatory conditions in current cancer patients compared to those without cancer (H. Ng et al., 2016). Ayeni et al. (2019) conducted a study on South African breast cancer patients and described that the most prevalent co-occurring chronic conditions were obesity (85%), hypertension (61%), impaired fasting glucose (47%), and depression (11%) (Ayeni et al., 2019). However, the prevalence of mood disorders including adjustment disorder, anxiety, and depression is reported to be as high as 38% among cancer patients compared to the global prevalence of 14% among the general population (Mitchell et al., 2011; Waraich et al., 2004).

2.3 Cancer Survival and Impact of Multimorbidity

Cancer survival varies by cancer type, clinical stages, as well as sociodemographic, and healthcare factors. For example, lung cancer has an extremely poor prognosis, with a median survival of one year (Tas et al., 2013). For colorectal cancer, 1-year survival is estimated at 97.7% with a diagnosis at stage 1 but falls to 43.9% when diagnosed at stage 4 (Hawkes, 2019). On the other hand, breast and prostate cancer have a much higher one and five-year survival. Patients diagnosed with stage 1, 2, or 3 prostate cancer have almost 100% one and five-year survival. However, if they are diagnosed at stage 4, the one and five-year survival decrease to 87.6% and 47.7%, respectively (Hawkes, 2019). In Canada, most breast cancers are diagnosed at stage 1, with an overall five-year survival of 84-88% (Canadian Cancer Society, 2018).

Age, sex, and ethnicity are important predictors of cancer survival (Neal & Allgar, 2005; Tas et al., 2013; E. T. Warner et al., 2015). A study conducted on lung cancer patients showed that the

one-year survival rate was 67.3% for younger and 42.5% for elderly patients; age remained a significant predictor of mortality after controlling for demographic and clinical variables (Tas et al., 2013). Another study on breast cancer assessing the role of ethnicity in cancer survival found that the black population had 21% more risk of death due to breast cancer compared to Caucasians; while Hispanics and Asian people had a 44% lower risk of breast cancer-related death (E. T. Warner et al., 2015). Socioeconomic conditions also influence survival for many cancers (Bermedo-Carrasco & Waldner, 2016; de Graeff et al., 2001; C. D. Hsu et al., 2017). Sociodemographic factors are related to the stage of cancer diagnosis, which may impact the survival (Arndt et al., 2001; C. D. Hsu et al., 2017; Neal & Allgar, 2005; Woods et al., 2006).

On the other hand, advanced cancer treatment modalities, for instance, chemotherapy, radiotherapy, hormonal treatment, immunotherapy, surgery, and early initiation of treatment contribute to improving cancer outcomes, survival, and patient's quality of life (Daneshi et al., 2018; Glimelius et al., 1996; Kopetz et al., 2009; Miller et al., 2019; Tsai et al., 2018). However, cancer and its treatment cause physical and psychosocial sequelae (Miller et al., 2019; Stanton et al., 2015); survivors of cancer have compromised physical, mental health, and lower quality of life (Stanton et al., 2015). Besides, cancer risk and mortality, as well as needs for resources, increase with MMB, the co-existence of multiple chronic conditions (Eibl et al., 2018; Johnson et al., 2016; Tu et al., 2018).

MMB impacts the timing of cancer diagnosis, complicates treatment with polypharmacy, and increases mortality among cancer patients (Sarfati et al., 2016; Cancer Care Ontario, 2018). While it is established that early detection leads to better outcomes, studies reported that comorbidities can lead to delayed screening procedures among women and increase the odds of late diagnosis of breast cancer (Gurney et al., 2015; D. F. Warner et al., 2017). However, one study reported higher

odds of screening mammography for breast cancer among women with MMB compared to those with no chronic conditions (Koroukian et al., 2018). In a cohort of lung cancer patients, comorbidity led to earlier diagnosis owing to frequent physician's visits (Dima et al., 2018).

The survival of cancer patients is influenced by the level of MMB (Dima et al., 2018; Jørgensen et al., 2012; Ording et al., 2013). Elderly lung, colorectal, and prostate cancer patients with MMB have a higher risk of mortality compared to those without any chronic conditions (Jørgensen et al., 2012). Besides, cancer patients with MMB have a lower quality of life (Fortin et al., 2004), higher functional impairment, and poorer self-reported health compared to those with no additional condition (D. F. Warner et al., 2017). MMB also adds to the treatment burden on cancer patients (Salako et al., 2018; Sarfati et al., 2016; Shrestha et al., 2019). Multimorbid cancer patients are less compliant with treatment, more prone to develop side-effects, likely to be prescribed multiple drugs (polypharmacy), have less access to curative cancer surgery, and become socially isolated (Corbett & Bridges, 2019; Ihemelandu et al., 2016; Ritchie et al., 2011). Arthritis is one of the most prevalent chronic conditions in cancer patients and it impacts patients' outcomes and care management (Nayak, Luo, Elting, Zhao, & Suarez-Almazor, 2017; Roy et al., 2018) as described in the following sections.

2.4 Arthritis

Arthritis is a clinical condition referring to joint disorders and is characterized by pain, swelling, and limitation of movement (Health Canada, 2003). It is a disease of the musculoskeletal system involving joints, ligaments, tendons, and bones (Health Canada, 2003). Arthritis causes pain, swelling, stiffness in joints, thereby leading to disability and decreased quality of life (Arthritis Alliance of Canada, 2011). Arthritis is one of the leading chronic diseases among adults.

In Canada, in 2011, 4.4 million adults (13% of the population) were living with osteoarthritis (Arthritis Alliance of Canada, 2011). It is estimated that by 2026, 6 million Canadians aged 15 or more will suffer from arthritis and related disorder (Health Canada, 2003). Arthritis is more common among the elderly, obese, and persons receiving hormone replacement therapy (Health Canada, 2003). The population prevalence of rheumatoid arthritis (RA) in Canada was 0.9% in 2011 and is expected to be 1.3% in the next 30 years (Arthritis Alliance of Canada, 2011).

Osteoarthritis (OA) is the most common type of arthritis, and it is particularly prevalent among the middle-aged and elderly population (American College of Rheumatology, 2019). OA involves the entire joint causing "wear and tear" of the joint structures and the lifetime risk of developing the condition is around 46% (American College of Rheumatology, 2019). Rheumatoid arthritis (RA) causes joint destruction and occurs in older adults (Helmick et al., 2008). Pain is the primary complaint in the majority of patients with arthritis, and levels of pain are twice as high in people with arthritis as in the general population (Health Canada, 2003). In their study on the quality of life of RA patients, Corbacho & Dapueto (2010) found that 60% of patients with RA had moderate to severe pain, and 70% of patients had some sort of disability (Corbacho & Dapueto, 2010). Arthritis causes limitations in daily activities, particularly among the elderly population around two-third of the patients with arthritis develop disability (Health Canada, 2003). However, more than half of the children with juvenile arthritis in Canada also mentioned problems with performing their daily activities (Health Canada, 2003). The patients with arthritis have an inferior self-reported health status, lower satisfaction while in different social roles, poor employment outcomes, and suffer from continuous fatigue, sleep disturbance, and stress (Health Canada, 2003; Gignac et al., 2008, 2018).

Risk factors for arthritis vary by the types of arthritis. Risk factors for OA and RA are increasing age, female sex, ethnicity, genetic factors, nutrition, obesity, metabolic diseases, smoking, osteoporosis, joint injury and decreased muscle function; particularly BMI >30, have been associated with 2.81 times higher probability of knee OA (Litwic et al., 2013; Xu & Lin, 2017). Aging affects joints through the inflammatory process and the majority of the people aged 65 or more have radiographic features of OA (D. Chen et al., 2017; Litwic et al., 2013).

Patients with inflammatory rheumatic conditions are more likely to present with MMB; for example, two-third of patients with rheumatoid arthritis have another comorbid condition (Filipowicz-Sosnowska, 2019; Radner, 2016). Comorbidities impact the disease course and outcomes in arthritic conditions leading to poorer prognosis (Filipowicz-Sosnowska, 2019). Literature suggests hypertension, hypercholesterolemia, diabetes, cardiovascular diseases, obesity, depression, and cancer as the commonly co-occurring conditions with rheumatic diseases (Filipowicz-Sosnowska, 2019; Radner, 2016). On the other hand, arthritis is one of the most common comorbidities occurring in cancer patients (Roy et al., 2018).

2.5 Arthritis and cancer

The relationship between cancer and arthritis is complex and multifactorial. Cancer and its treatment impact the outcomes of patients with arthritis (Almoallim et al., 2017; Andrykowski et al., 1999; Elandt & Aletaha, 2011; Naidoo et al., 2017; D. D. Yang et al., 2018), whereas, in some instances, arthritis can be a risk factor for cancer (Askling et al., 2005; Y.-J. Chen et al., 2011; Lewis et al., 2018; Mellemkjaer et al., 1996; Rohekar et al., 2008; Wilton & Matteson, 2017). In a population-based cohort study, it was found that the risk of Hodgkin and Non-Hodgkin lymphoma, lung, and skin cancer was higher among RA patients; however, the risk for colorectal and breast cancer was reduced (Mellemkjaer et al., 1996). Hellgren and Colleagues (2010) found a 1.75 times

higher risk of lymphoma in RA patients and concluded that inflammation, immunosuppressive treatment, genetic, and environmental factors might explain the higher occurrence of cancers in patients with RA (Hellgren et al., 2010). In a retrospective population-based cohort study Ward & Alehashemi, (2020) found that knee and hip osteoarthritis was related to increased risk of melanoma, renal cancer, and cancer of the bladder, breast, uterus, and prostate while lowering the risk of the oropharynx, esophagus, stomach, colon/rectum, hepatobiliary, pancreas, larynx, lung, and ovarian cancer (Ward & Alehashemi, 2020). However, the risk of specific cancers increased with the duration of osteoarthritis (Turkiewicz et al., 2020). Researchers mentioned that lower expression of a protein, Chondromodulin-1, might be the link between the pathogenesis of cancer and OA (Zhu et al., 2019).

The treatment of arthritis may also contribute to the development of cancer. Patients receiving cyclophosphamide, a drug used for RA, predispose them to the risk of bladder cancer (Wilton & Matteson, 2017). On the other hand, the cancer treatment has been linked to developing arthritis by several authors (Almoallim et al., 2017; Andrykowski et al., 1999; Naidoo et al., 2017; D. D. Yang et al., 2018). In a study conducted on prostate cancer patients, researchers found a 23% increased risk of developing RA among patients treated with androgen deprivation therapy (D. D. Yang et al., 2018). In their review article, Naidoo et al. (2017) described that there might be an association between cancer treatment with immune checkpoint blocking and the development of post-treatment arthralgia or inflammatory arthritis (Naidoo et al., 2017).

The impact of arthritis on cancer outcomes has been addressed in several studies (Ji, Liu, Sundquist, & Sundquist, 2011; Nayak et al., 2017). In a large population-based retrospective cohort study in the United States, breast cancer patients with two or more claims for RA in the last 12 months had 41% higher mortality than those without an RA diagnosis (Nayak et al., 2017). In

prostate cancer patients, people with RA had 53% higher mortality considering the disease stage and tumor size (Nayak et al., 2017). Another study in Sweden reported similar findings (Ji et al., 2011); they reported a 31% higher mortality in cancer patients hospitalized with RA compared to those without RA. The lowest survival was found in skin, breast cancer, and non-Hodgkin lymphoma in patients with RA (Ji et al., 2011).

As mentioned above, mood disorders are commonly occurring comorbidities with arthritis, with or without cancer, and may also affect the role of arthritis. The relationships between arthritis, mood disorders, and cancer are described in detail below.

2.5.1 The role of arthritis in developing mood disorders

The prevalence of mood disorders is 45% among the patients with RA and the prevalence of depression is as high as 61% in patients with OA (Leite et al., 2011; Nicassio, 2010). A study conducted by He et al. (2008) found that patients with arthritis had 1.9 times higher odds of mood disorders compared to the general population (He et al., 2008). Another retrospective cohort study revealed that patients with RA had twice the risk of developing bipolar disorder than people without RA (Hsu et al., 2014) The risk of depressive symptoms increases with disease severity among OA patients (Rathbun et al., 2018). The pain and disability are significantly related to mood disorders and among the working population with arthritis pain is a predictor of developing depressive symptoms (Li et al., 2006; Nicassio, 2010; Parmelee et al., 2012). However, a recent study suggests that arthritis and mood disorders have a shared pathological process as both conditions are characterized by inflammation (Vallerand et al., 2019). Arthritis patients with co-occurring mood disorders are more likely to experience increased pain, disability, and decreased activity (Marks, 2014; Sharma et al., 2016; Sturgeon et al., 2016; Tsuchiya et al., 2014). Patients

with arthritis and depression are at increased risk of polypharmacy and are high users of health services (Sharma et al., 2016; Vergés Milano et al., 2016).

2.6 Mood Disorders

"Mood disorders are psychiatric conditions in which the principal feature is a prolonged pervasive emotional disturbance, such as a depressive disorder, bipolar disorder, or substance-induced mood disorders. The term 'chronic mood disorders' is applied when symptoms rarely remit" (American Psychiatric Association Dictionary, 2018). According to the World Health Organization, around 310 million people were suffering from depression and bipolar disorder globally in 2018, which made it one of the significant contributors to the global disease burden (World Health Organization, 2018). In Canada, in 2018, around 2,802,000 people were suffering from any kind of mood disorder which was 8.9% of the population aged 12 or older (Statistics Canada, 2020). The annual prevalence of depression in Canada was 4.7% in 2012, and Canadians had a lifetime prevalence of 11.2%. (Knoll & MacLennan, 2017). Among patients with cancer or arthritis in Canada, the prevalence of mood disorders in 2005 was 10.1% and 10.9%, respectively (Gadalla, 2008). Bipolar disorders are relatively uncommon and a cross-sectional survey conducted in 11 countries reports that the lifetime prevalence of developing bipolar disorder is 2.4% (Rowland & Marwaha, 2018). Another study reported that the prevalence of self-reported bipolar disorders was only 0.87% in Canada (McDonald et al., 2015). However, a portion of patients diagnosed and treated for major depressive disorders may also have co-occurring bipolar disorder (Rybakowski et al., 2005). Mood disorders, particularly depression, are more common among people who are females, separated, unemployed, and those with chronic diseases; with the peak incidence found in ages15-24 years (Gadalla, 2008; Scott B. Patten et al., 2006). On the other hand, bipolar disorders are linked with several genetic and environmental factors, but no

significant established environmental and genetic risk factors were found for bipolar disorder (Rowland & Marwaha, 2018b).

2.7 Mood disorders in cancer patients

Psychiatric disorders are common among patients with cancer. In a systematic review, the authors reported that the prevalence of mental health conditions in cancer patients was around 32% (95% confidence interval 27% to 37%) (Singer et al., 2010). Around 97.5% of cancer patients attending psychiatric outpatient departments receive a diagnosis of a psychiatric condition and the prevalence of mood disorders is as high as 18-29% (Anuk et al., 2019; Mitchell et al., 2011). Several studies have reported a higher prevalence of depression among cancer patients than the general population (Hartung et al., 2017; Pitman et al., 2018; Yang et al., 2013). A study conducted in Germany detected 5.4 times higher odds of depression among cancer patients than the general population estimate (Hartung et al., 2017). However, there are substantial variations in the prevalence of depression due to the different scales used to quantify depression and depressive symptoms (Caruso et al., 2017; Krebber et al., 2014), varying between 10% and 25% for most studies (Hartung et al., 2017; Knoll & MacLennan, 2017; Ng et al., 2011; Nikbakhsh et al., 2014; Pitman et al., 2018; Walker et al., 2013; Walker et al., 2014), and reaching 76% for patients with oesophageal cancer (Chung et al., 2018; Hong & Tian, 2014; Massie, 2004; Shankar et al., 2016; Yang et al., 2013). On the other hand, mood disorders, particularly bipolar disorder have been associated with an increased risk of cancer (BarChana et al., 2008; Lin et al., 2013). However, there is little evidence found in the literature regarding the increased risk of bipolar disorders in cancer patients.

The development of mood disorders varies by cancer type. For example, patients with cancer in the head-neck region have a prevalence of depression as high as 50% (Yadav et al., 2019), and

depression is most common among patients with pancreatic, gastric, lung, colorectal, breast, and genitourinary cancer (Chung et al., 2018; Massie, 2004; Shankar et al., 2016; Jane Walker et al., 2014). Major depressive disorder (MDD) is mostly found among cancer patients in palliative care (J. Walker et al., 2013), having other psychological or medical conditions (Hartung et al., 2017; Massie, 2004) and with late-stage metastatic carcinoma (Hartung et al., 2017). Caruso et al. (2017) conducted a meta-analysis and described that family history of mood disorders, female sex, and poor support act as potential risk factors for depressive spectrum disorders in cancer patients (Caruso et al., 2017). Breast cancer patients undergoing mastectomy fear a change in their body image, and up to 50% of them may develop symptoms of anxiety and mood disorders (Lasry et al., 1987; Pan et al., 2016). Pirl & Roth (1999) performed a systematic review and concluded that uncontrolled pain was the primary cause of depression in cancer patients; recognizing the pain and attempting to relieve the pain improved depression symptoms in those patients (Pirl & Roth, 1999). Alemayehu and colleagues (2018) found a four times higher risk of depression among cancer patients who complained of moderate pain and thirteen times higher risk of depression with severe pain (Alemayehu et al., 2018). Cancer treatment including medication, chemotherapy, and advanced immune therapies are also responsible for causing depressive spectrum disorders (Caruso et al., 2017; Scott B. Patten & Barbui, 2004; Pirl & Roth, 1999; Smith, 2015). MMB in cancer patients is a predictor of mood disorders. For example, depression is often found in combination with neurological, endocrine, and inflammatory diseases (Pirl & Roth, 1999; Smith, 2015). Literature suggests that cancer causes altered stress response resulting in the alteration of neuroendocrine pathways which ultimately lead to the development of depressive spectrum disorders (Caruso et al., 2017; Postal & Appenzeller, 2015; Young et al., 2014).

The presence of depression in cancer patients and its association with higher mortality is addressed in the literature (Iglay et al., 2017; Pinquart & Duberstein, 2010; Satin et al., 2009). A study conducted on breast cancer patients with mood disorders revealed that patients with depression had a 1.33 (95% CI: 1.20–1.48) times higher risk of mortality than those without any mood disorders but no significant difference in survival was found for the patients with bipolar disorders (Kanani et al., 2016). The association between mood disorders particularly depression and higher mortality are evident for all cancer sites, including lung, breast, gastrointestinal, and other cancer sites (Onitilo et al., 2006). Depression causes late diagnosis of cancer as well as an interruption, lower acceptance of, and less response to treatment (Colleoni et al., 2000; J. Lin et al., 2016; Pinquart & Duberstein, 2010; Zimmaro et al., 2018). Nielson and colleagues (2019) determine that elderly cancer patients with bipolar disorders receive treatment at a later stage, impacting their survival (Nielsen et al., 2019). Several other studies also linked bipolar disorders with increased mortality in cancer patients (Chang et al., 2014; Kanani et al., 2016).

Depression, one of the most prevalent mood disorders has been linked to the quality of life of cancer survivors by several authors (Khue et al., 2019; Q. Li et al., 2018; Rolke et al., 2008; Smith, 2015; Villarreal-Garza et al., 2019). Khue et al. (2019) conducted a study on lung cancer patients in Vietnam and revealed that health-related quality of life was significantly lower among those who were depressed compared to the patients without depression (Khue et al., 2019). Depression raises the tendency of suicide, especially among cancer patients with poor social support (Dauchy et al., 2013).

The management of mood disorders in cancer patients is complex and requires integrated pharmacologic and psychological intervention (M. Li et al., 2016; Mehta & Roth, 2015). Cancer patients are sometimes widely prescribed with antidepressants leading to polypharmacy

(Desplenter et al., 2012). However, there is also a risk of inadequate treatment in cancer patients with depression (Jane Walker et al., 2014). In a population-based study in Denmark, Y. Sun et al. (2015) found that treatment of depression with antidepressant drugs caused 32% higher one-year and 22% higher five-years mortality (Y. Sun et al., 2015). In cancer patients with bipolar disorders or mania, the choice of antipsychotic drugs should be made carefully according to the severity of the disease and symptoms; long term use of such drugs may lead to complications (Mehta & Roth, 2015).

In summary, arthritis and mood disorders contribute to worse outcomes, such as lower survival and lower quality of life among cancer patients, and the impact may be exacerbated when they are both present. Hence, it is important to study and monitor the risk of mood disorders among cancer patients for their well-being. A key outcome is the utilization of health services by cancer patients, which impacts both the individual and the healthcare system.

2.8 Health Care Utilization (HCU)

Health care service utilization has been modeled in various ways, but the Anderson Behavioral Model is one of the most widely used models (Babitsch et al., 2012). A person's HCU is determined by the methods of delivery of the services, changing medical technologies, social definition of the disease, and by the individual predisposing, enabling, and need factors (R. Andersen & Newman, 2005). HCU is particularly high among males, unmarried patients, persons with comorbidities, psychological disorders, persons who smoke or drink alcohol, or have chronic pain (Graham et al., 2019). HCU can be measured from two perspectives: quantity and quality (Da Silva et al., 2011). Quantitative indicators of HCU include hospitalization per year, the number of patients and visits, whereas the quality indicators include accessibility, continuity, comprehensiveness, and productivity of care (Da Silva et al., 2011).

2.8.1 Cancer and health care utilization: role of arthritis and mood disorders

Cancer patients represent the highest users of the health care system, and many factors determine their HCU. In Ontario, approximately one-third of cancer patients had other chronic conditions besides cancer, and these represented the top 10% of the health care users (ICES, 2014). In a population-based study on data from the Eindhoven Cancer Registry, Mols et al. (2007) described that cancer survivors had more general and specialist physicians' visits than the general population. In particular, HCU was highest among Hodgkin's lymphoma patients and in patients with comorbidities (Mols et al., 2007). In cancer patients, the co-occurrence of chronic conditions was associated with increased physician's visit (Arreskov et al., 2018; Duthie et al., 2017; Kent et al., 2018). Lash et al. (2017) conducted a systematic review and reported that there was a variation in the percentage of cancer patients having at least one ED visit, ranging from 7-12% across the studies. ED visits were highest among female reproductive organ cancer patients, followed by colorectal, prostate, lung, and breast cancer (Lash et al., 2017). They also found that ED visits were more common among cancer patients with African-American ethnicity, advanced age, male gender, residing in an urban area, being unmarried, having severe symptoms, stage III or IV cancer, comorbidities, and who survived at least one year after cancer diagnosis (Lash et al., 2017).

MMB, especially common comorbidities such as arthritis and mood disorders impacts health care utilization among cancer patients (Himelhoch et al., 2004; Pitman et al., 2018; Roy et al., 2018; Wright et al., 2010). In their study, Wright et al. (2010) found that patients with knee osteoarthritis had higher health care utilization compared to those without OA, and the HCU increased with the presence of comorbidities including cancer (Wright et al., 2010).

Several studies have addressed the impact of mood disorders on HCU by cancer patients (Himelhoch et al., 2004a; Mausbach & Irwin, 2017; McDermott et al., 2018a; Niazi et al., 2018).

Niazi et al. (2018) described that multiple myeloma patients with comorbid mood disorders had 41% more hospitalizations, 37% higher ED visits, and 22% higher ambulatory service usage than patients without mood disorders (Niazi et al., 2018). Patel and colleagues (2018) conducted a study on breast, prostate, colorectal, and lung cancer patients in the United States to reveal the impact of MDD on patient outcomes. They found that cancer patients with MDD had a significantly higher mean hospital stay across all four cancer types (Patel et al., 2018). Cancer patients with pre-existing depression have lower odds of inpatient visits, ED visits, and ICU admission than patients without depression; however, when depression was diagnosed after cancer, an increase in HCU was found, but not statistically significant (McDermott et al., 2018). Although several studies focused on HCU by cancer patients, there is still inadequate evidence of the impact of MMB, especially the occurrence of arthritis and mood disorders on health service usage among cancer patients in Canada. This research will address the impact of arthritis and mood disorders on the HCU of cancer patients in Ontario at the population level.

Chapter 3: Thesis Methodology Overview

The literature review suggested that mood disorders are prevalent among cancer patients and have a negative impact on cancer outcomes. It is also known that cancer patients with multimorbidity are more prone to develop mood disorders, particularly depression. However, the combined role of arthritis and MMB on the development of mood disorders in cancer patients is still not clearly described, and this thesis is aimed to address those gaps in the literature. Understanding the effect of arthritis and MMB on the development of mood disorders will help to detect cancer patients most vulnerable to developing psychological morbidities.

3.1 Objectives

The primary objective of this research is to measure the incidence of mood disorders among cancer patients in Ontario, Canada, and to assess the associated sociodemographic and clinical factors, including multimorbidity and in particular, comorbid arthritis as an example of inflammatory disease, associated with mood disorders among people with cancer. This study also aims to evaluate health service utilization among cancer patients with multimorbidity, particularly arthritis and mood disorders. The specific research questions are-

1. What is the incidence of mood disorders among cancer patients in Ontario?
    a. Does arthritis increase the risk of mood disorders in cancer patients?
    b. What is the impact of arthritis on the development of mood disorders in cancer patients at different levels of multimorbidity?
2. Do arthritis and mood disorders increase health care utilization in cancer patients?
    a. How does the impact of arthritis and mood disorders on health care utilization among cancer patients vary by level of multimorbidity?

3.2 Approach to Thesis

This study aims to determine the impact of arthritis (exposure) on the development of mood disorders (outcome) in cancer patients while accounting for the role of sociodemographic factors and the level of multimorbidity**.** In the second part of the study, we looked at the role of arthritis and mood disorders (exposures) on the health service utilization among cancer patients in terms of hospitalizations and emergency (ED) visits (outcomes) considering the level of multimorbidity. A quantitative study with health administrative data in Canada was designed to answer the research questions. The conceptual framework of this study was based on Andersen's Behavioral Model of Health Services Use (R. M. Andersen, 1995). The model suggests that HCU is a function of several predisposing, enabling, and need factors (R. M. Andersen, 1995). The predisposing factors determine the likelihood that people will need the health care system and include social structures like education, occupation, ethnicity, social interactions, culture or health beliefs, or demographic variables such as age and sex (R. M. Andersen, 1995). The enabling factors are the people's and community's capability and resources for using the health care system. These factors are comprised of personal/family factors like health insurance, knowledge of access to care, traveling or community factors, or genetic and psychological attributes (R. M. Andersen, 1995). The need factors are either perceived by the patients arising from the symptoms of the disease and pain or evaluated needs based on professional judgment. The need factors raise people's demand for health care (R. M. Andersen, 1995).

For the proposed project, predisposing factors included age, sex, and ethnic concentration. The enabling factors were income and the place of residence (rural/urban), while chronic conditions, namely cancer, arthritis, and mood disorders acted as the health care need factors.

3.3 Hypothesis

Hypothesis#1: Arthritis increases the risk of mood disorders among cancer patients and the presence of other comorbidities exacerbates the risk.

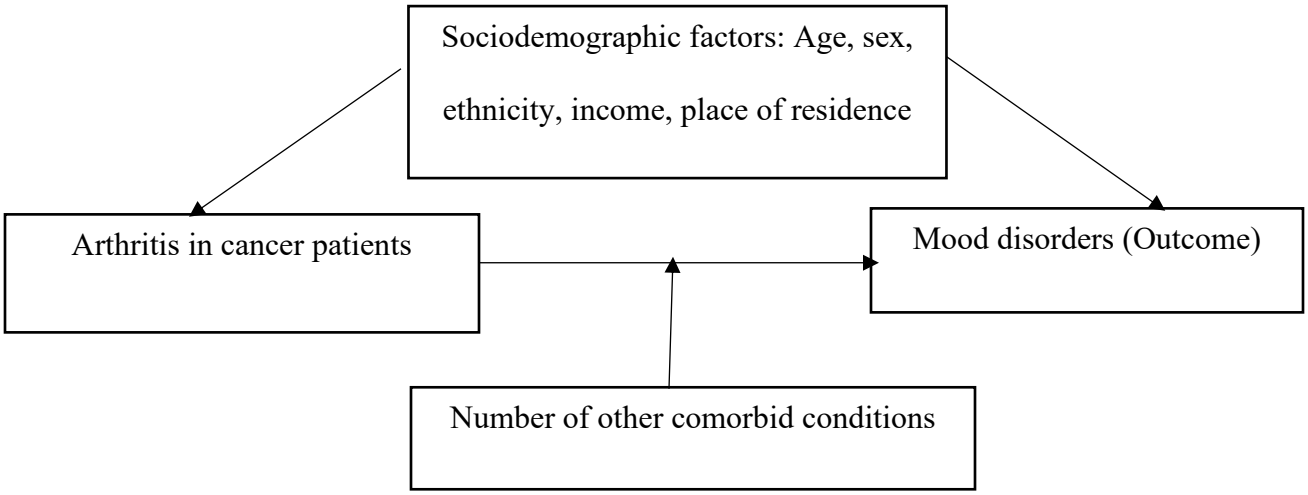


Fig 1: Impact of arthritis on the development of mood disorders considering the sociodemographic and clinical factors

Hypothesis#2: Arthritis and mood disorders increase the health care utilization (hospitalizations and ED visits) among cancer patients; the co-occurrence of other comorbid conditions further increases HCU.

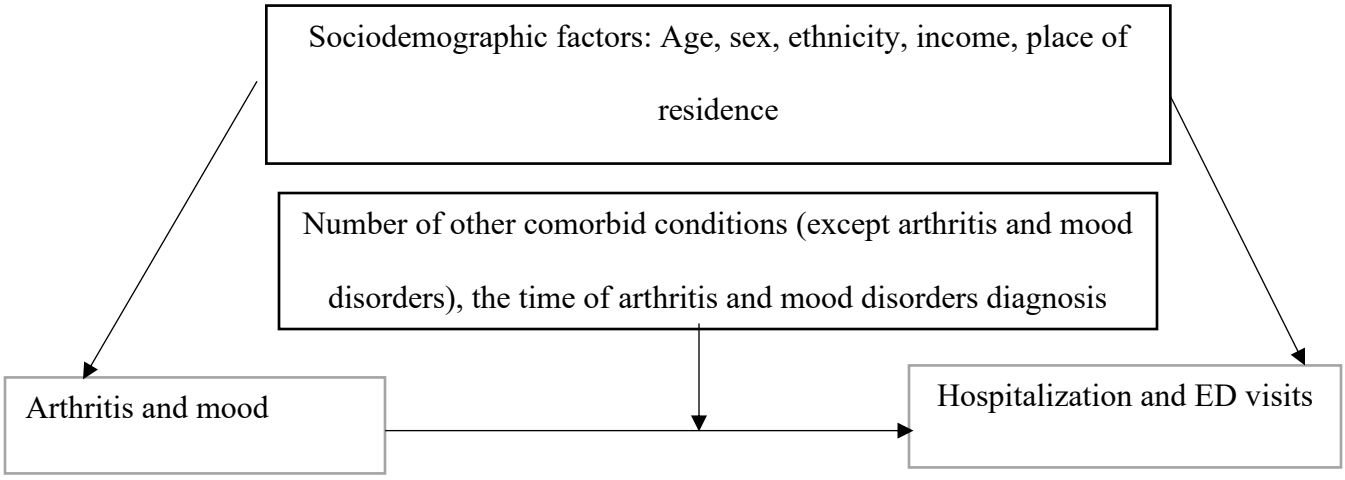


Fig 2: Impact of arthritis and mood disorders on the HCU by cancer patients

3.4 Study Design and Population

We used a retrospective cohort study based on health administrative data to describe the impacts of arthritis and MMB on the development of mood disorders in cancer patients. The design helped to determine if a causal relationship exists, and helped validate our assumptions about the association between arthritis, MMB, and mood disorders in patients with cancer (Luisa Vázquez Navarrete, 2009). All the adult patients diagnosed with cancer in Ontario between 2003-13 without pre-existing mood disorders and who survived at least a year after their cancer diagnosis were included as the study population. We further performed another retrospective cohort study with the same databases and included all the adult patients having cancer between 2003-13 and surviving at least a year to evaluate the effect of arthritis and mood disorders on the hospitalization and ED visits following cancer diagnosis considering the number of other comorbid conditions.

3.5 Data Sources

This study was based on provincial administrative databases in Ontario that were linked to define the study population and outcome of interest. These datasets are housed at the Institute for Clinical Evaluative Sciences (ICES) and include information on health services utilization, disease registries, and basic population characteristics. All the residents of Ontario, including immigrants after their three months mandatory waiting period, are covered by provincial health insurance and are assigned a unique health card number. ICES is authorized to access, link, and analyze health administrative data for evidence generation and reforming policies (Ishiguro et al., 2016). The specific databases used for this study included the Ontario Cancer Registry (OCR), Ontario Health Insurance Plan (OHIP), Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), and the Registered Person Database (RPDB).

The Ontario Cancer Registry (OCR) contains information about all the patients diagnosed with cancer or who died from the disease from 1964 to 2018 (Cancer Care Ontario, 2018). It includes the type of cancer, age at diagnosis, sex, and the date of a cancer diagnosis. The data in this registry are collected from hospital admission, pathology, physician's consultation, and death certificates (Cancer Care Ontario, n.d.). The morphology and typology codes and stages of cancer were obtained from the Ontario Cancer Registry (OCR). The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) coding system were used to group these codes into types such as breast, lung, colorectal, prostate, urinary system, hematological, female reproductive system, digestive system except colon and rectum, etc. (National Cancer Institute, 2008).

The Ontario Health Insurance Plan (OHIP) claims contain data about the physician's visits with the diagnosis and the procedures performed (Cadarette & Wong, 2015). The Discharge Abstract Database (DAD) contains inpatient data from hospitals, including the date of admission, discharge, length of stay, diagnosis, and procedures (Cadarette & Wong, 2015). The National Ambulatory Care Reporting System (NACRS) encompasses the hospital outpatient data, emergency visits, and day surgery procedures (Cadarette & Wong, 2015). The data for the diagnosis of mood disorders, arthritis, and other chronic conditions were derived from these three databases. The hospitalization data were obtained from the Discharge Abstract Database (DAD) and emergency visits data from the National Ambulatory Care Reporting System (NACRS) databases.

The Registered Person Database (RPDB), which is comprised of the demographic data of persons enrolled in the Ontario Health Insurance Plan, was used to identify the patient's age, sex, income quintile, and place of residence. The unique encrypted patient identifier in the RPDB and all health data allow for record linkage across all the databases (Cadarette & Wong, 2015). The

place of residence (rural/urban) and the neighborhood income quintiles were derived from the RPDB. The rurality index of 0 to 39 is considered as urban and 40 or more as rural.

The Ontario Marginalization Index (ON-Marg) is a measure of inequalities between the geographical areas based on four dimensions; residential instability, material deprivation, ethnic concentration, and dependency (Matheson et al., 2012). For our study purpose, we only considered the ethnic concentration quintiles, a higher value indicated a higher proportion of recent immigrants (arrived in Canada within the last five years of the census), and self-identified visible minorities (Matheson et al., 2012). The detailed description of the databases and related variables is summarized in table 1.

Table 1

Administrative databases used for the study and the corresponding study variables

Database	Description	Variables
Registered Persons Database (RPDB)	Includes data on all person eligible for the Ontario Provincial Health care program and provides demographic information like age, sex, date of birth, death, residence, and neighborhood income	Age, sex, residence, income quintile
Discharge Abstract Database (DAD)	Hospital inpatient data. It includes data on hospital admission, discharge, length of stay, primary diagnosis, other diagnoses, procedures, and interventions	Arthritis, mood disorders, and other comorbidities using the ICD codes, date/year of diagnosis, hospitalization

Ontario Health Insurance Plan (OHIP) claims	Physician's claim database. Includes the date of visit, diagnosis, procedures such as laboratory tests and vaccination	Arthritis, mood disorders, and other comorbidities using the ICD codes, date/year of diagnosis
National Ambulatory Care Reporting System (NACRS)	Includes hospital outpatient data, diagnosis, day surgeries, and Emergency department visits	Arthritis, mood disorders, and other comorbidities using the ICD codes, date/year of diagnosis, ED visits
Ontario Cancer Registry (OCR)	Provincial database of all the residents of Ontario having a diagnosis of cancer. Contains demographic and clinical information including the date of diagnosis, primary cancer site, cancer stage, and death	Age, sex, date of birth, death, cancer type, date of cancer diagnosis

3.6 Ethical Considerations

This study was a part of the research project titled "Support complex cancer patients with multimorbidity navigate efficiently between health care and cancer care systems." Ethics approval for the project was obtained from the Lakehead University Research Ethics Board and ICES. As the study is based on the administrative databases, informed consent is not required. An ethics waiver from the Lakehead University research ethics board was obtained for this thesis. All the data are secured at ICES, and the researchers use a secure user interface ICES Data and Analytic Services Environment (IDAVE) for accessing and analyzing the data. IDAVE provides a secure

virtual interface where all accredited researchers can analyze data with the provided software, and the aggregate results are released only after being vetted by ICES, to maintain the privacy and the security of the data.

Chapter 4: Impact of Arthritis on the Development of Mood Disorders in Cancer Patients: A Population-based Retrospective Cohort Study

Abstract

Objectives: This study aimed to explore the impact of arthritis on the risk of developing mood disorders among cancer patients with or without other comorbidities.

Method: A retrospective population-based cohort study with linked health administrative data was conducted. Ontarians diagnosed with cancer between 2003 and 2013 were followed up until March 2018. Those with pre-existing mood disorders were excluded. The incidence of mood disorders was compared between cancer patients with and without arthritis. Survival analysis using Cox proportional hazard modeling was performed to assess the adjusted impact of arthritis on the development of mood disorders, considering multimorbidity (MMB) and other sociodemographic and clinical factors.

Results: The cohort included 444,552 participants, aged 63 years on average; 51% had arthritis. The cumulative incidence of mood disorders was 16.9 (95% CI 16.6-17.3)/1,000 patients, and respectively 17.0 (95% CI 16.5-17.6) and 16.8 (95% CI 16.3-17.3) per 1,000 in patients with and without arthritis. In the adjusted Cox model, there was no significant difference in the risk of developing mood disorders among patients with or without arthritis. The risk of mood disorders was higher among males, patients with lung cancer, and patients in stage IV cancer; it increased with the level of multimorbidity. The association between arthritis and mood disorders was not impacted by the number of other comorbidities.

Conclusion: The findings showed that arthritis was not associated with increased risk of mood disorders, but MMB was a significant risk factor. The study provides evidence for addressing multimorbidity among cancer patients to reduce their risk of developing mood disorders as well as other psychologic conditions, in order to potentially improve their outcomes.

Introduction

Mood disorders are a great concern among cancer patients as it impacts their survival, quality of life, and care management (Kanani et al., 2016; Pinquart & Duberstein, 2010; Pitman et al., 2018). In fact, such disorders are quite prevalent in cancer patients and result in reduced survival given that depression alters the neuroendocrine and immunological process of the body (Spiegel & Giese-Davis, 2003). The prevalence of depressive disorders ranged from 5-60% among cancer patients depending on the methods used for diagnosis (Caruso et al., 2017). In a systematic review, it was reported that among hospitalized cancer patients, the prevalence of major depressive disorder (MDD) was 14-30%, whereas, in cancer outpatients, the MDD prevalence was 5-16% (Walker et al., 2014). Cancer recurrence, comorbidities, past psychiatric conditions, advanced cancer with metastasis, poor social support, low socio-economic condition, and being single represent contributing factors for developing mood disorders (Anuk et al., 2019).

In Canada, the life expectancy of cancer survivors has increased from 55 years to 63 years from 1990 to 2019 (Canadian Cancer Society, 2019). As such, multimorbidity (MMB), i.e. the occurrence of two or more chronic conditions is common among cancer patients (Koné Pefoyo et al., 2015). More than 75% of cancer patients in Ontario had additional comorbidities and the prevalence of MMB can reach up to 92% among the elderly population (Koné Pefoyo et al., 2015; Williams et al., 2018). Commonly occurring chronic conditions in cancer patients are hypertension, diabetes, musculoskeletal diseases including arthritis, heart failure, anxiety, and dementia which may be partly explained by their mutual risk factors with cancer (Gallacher et al., 2018; Johnson et al., 2016; Luque-Fernandez et al., 2019; Salako et al., 2018). Specifically, arthritis and cancer have shared pathological pathways (Yu et al., 2016). For example, the

incidence of rheumatic symptoms was significantly higher among breast cancer patients compared to those with benign breast disease (Andrykowski et al., 1999).

On the other hand, several studies linked arthritis with mood disorders, such as depression (Dickens et al., 2002; Husaini & Moore, 1990; Margaretten et al., 2011; Stubbs et al., 2016). Patients with arthritis are more likely to have mood disorders, particularly depression (Husaini & Moore, 1990) and at least 17% of rheumatoid arthritis patients had a diagnosis of major depressive disorder (Alpay, 2000; Sturgeon et al., 2016). In summary, MMB contributes to the complexity of cancer patients, especially mood disorders can have an important impact on cancer outcomes, while arthritis, one of the most common co-occurring conditions, may contribute to increasing the risk of mood disorders in cancer patients. This paper aimed to assess the influence of arthritis on the development of mood disorders among cancer patients in Ontario, Canada. We also described whether MMB mediates the association between arthritis and mood disorders in cancer patients.

Methods

Study Design and Data Sources

A retrospective cohort study with health administrative data from the Institute for Clinical Evaluative Sciences (ICES) was conducted to assess the effect of arthritis, sociodemographic, and other clinical factors on the development of mood disorders in cancer patients. In Ontario, all residents are eligible for health coverage and issued a unique health card number, including immigrants after their three months mandatory initial waiting period. The specific databases used for this study included the Ontario Cancer Registry (OCR), Ontario Health Insurance Plan (OHIP), Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), and the Registered Person Database (RPDB). The detail of the databases is provided in appendix A.

The study investigators obtained ethics approval from ICES and Lakehead University Research Ethics Board.

Study Population

The study cohort included all adults (aged 18 or older) in Ontario, who were diagnosed with cancer between April 1, 2003, and March 31, 2013, and who did not have any pre-existing mood disorders (as defined below) to ensure an accurate calculation of the incidence of mood disorders. Patients who had died within the first year of cancer diagnosis were excluded to avoid underestimation of the incidence of mood disorders, as it may take longer to identify and diagnose mental illness after a cancer diagnosis. Moreover, the severity and poor prognosis of certain types of cancer might take precedence leading to ignorance of the symptoms of mood disorders including depression among these patients masking the association between arthritis and mood disorders. The cohort was followed up until March 31, 2018, to identify the occurrence of 18 predefined chronic conditions including mood disorders.

Study Measurements

The primary exposure of the study was the presence of arthritis (both osteoarthritis and rheumatoid arthritis were considered together), at any time during the study period, but prior to mood disorders occurrence, which was a binary variable (yes/no). To identify cases of arthritis, ICD-9 codes from OHIP or ICD-10 codes in DAD or NACRS were used (Appendix B); a patient was deemed to have arthritis if he/she had at least two physician's claims with arthritis within a two-year period or one hospital admission or emergency visit with arthritis in one year. When rheumatoid arthritis (RA) is identified using one hospitalization ever or two physician's visit within a two year period, Canadian administrative databases have 83% sensitivity and 99%

specificity (Widdifield et al., 2014). On the other hand, when osteoarthritis (OA) is diagnosed using the definition stated above, administrative databases have low sensitivity but high specificity (Shrestha et al., 2016).

We were also interested in the impact of MMB on the study outcomes. Besides cancer, arthritis, and mood disorders, the chronic conditions included in the study were acute myocardial infarction (AMI), asthma, cardiac arrhythmia, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), chronic coronary syndrome, dementia, diabetes, hypertension (HTN), other mental illnesses, osteoporosis, renal failure, and stroke. These conditions were defined using validated algorithms where applicable or considering at least two physician's billing claims (OHIP) or one hospitalization (DAD or NACRS) for other conditions (Austin et al., 2002; A. S. Gershon et al., 2009; Andrea S Gershon et al., 2009; Hux et al., 2002; Jaakkimainen et al., 2016; Schultz et al., 2013; Tu et al., 2007). The chronic conditions included in this study were chosen based on their population burden and associated cost (Koné Pefoyo et al., 2015; Woodchis et al., 2016). The ICD codes for identifying the selected chronic conditions are provided in Appendix B. We counted the number of chronic conditions and classified as no conditions, 1, 2, 3, and 4 or more conditions.

The outcome was the time to development of mood disorders in cancer patients following a cancer diagnosis. Mood disorders were measured using specific ICD-9 and ICD-10 codes in OHIP, DAD, and NACRS (Appendix B). The patients were considered to have mood disorders whey they had at least two claims with mood disorders in OHIP in the last two years or one registration with DAD or NACRS in the previous one year. A study conducted by Fiest et al. (2014) described that if cases of depression were diagnosed using the case definition of one or more hospital admission in one year or 2 or more physician’s claims in two years, the sensitivity of DAD and OHIP database is 75% and specificity is 93% for diagnosing depression (Fiest et al., 2014). Other covariates

included in the study consisted of age, sex, ethnicity, place of residence, income quintile, cancer types, and stage. Age, sex, and the morphology and typology codes using The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) coding system and stages of cancer were derived from the Ontario Cancer Registry (OCR) (National Cancer Institute, 2008). Ethnic concentration quintiles were obtained from the Ontario Marginalization Index (ON-Marg) and a higher value (Q1 to Q5) indicated a higher proportion of recent immigrants, and self-identified visible minorities (Matheson et al., 2012). The place of residence (rural/urban) and the neighborhood income quintiles were derived from the RPDB. A rurality index of 0 to 39 were considered as urban and 40 or more as rural. Neighborhood income quintiles are based on census data; quintile 1 (Q1) has the lowest and quintile 5 (Q5) has the highest income (Specifications, n.d.).

Analyses

All the statistical analyses were performed using SAS software (SAS Institute, n.d.), on the remote secured ICES platform. Descriptive and bivariate analyses were used to describe the study population's demographic and clinical characteristics as well as to assess the relationship between the patient's sociodemographic characteristics, cancer type, number of other comorbidities, arthritis, and the development of mood disorders. The crude incidence of mood disorders was calculated and compared between cancer patients with or without pre-existing arthritis. We constructed a Kaplan-Meier curve and performed a log-rank test to identify the crude impact of arthritis (exposure) on time to the development of mood disorders (outcome) in cancer patients. Finally, a Cox proportional hazard model was fitted to study the adjusted effect of arthritis on the development of mood disorders. To investigate whether the role of arthritis on the development of mood disorders was modified by the number of other comorbid conditions, an interaction term

between arthritis and the number of chronic conditions was tested in the model. The model was also stratified by cancer type to evaluate whether the impact of arthritis on the development of mood disorders varied by cancer types (effect modification).

Results

The study included 444,552 adult patients with cancer living in Ontario, who survived at least one year after their cancer diagnosis and did not have any pre-existing mood disorders. The mean age of the population was 63.2 years, most had breast, colorectal, or prostate cancer. Around 87% of the patients had MMB, and 50.77% had a diagnosis of arthritis (Table 1). The association between sociodemographic and clinical characteristics and arthritis are also described in Table 1. The patients with arthritis were older, and more likely to have additional conditions, mostly female, from a higher sociodemographic background, and had mostly breast or prostate cancer.

Table 1.

Characteristics of the study population in general, and by arthritis status, N = 444,552

Characteristics	Total N= 444,552 (%)	With arthritis prior to mood disorders N = 225,697 (%)	Without arthritis prior to mood disorders N = 218,855 (%)	P-value
Arthritis prior to mood disorders				-
Yes	50.8	100	-	
Age at cancer diagnosis (years)				<0.0001
Mean (SD)	63.2 ± 14.2	65.6 ± 12.9	60.7 ± 14.9	
Range (min-max)	18-103	18-103	18-103	
Sex				<0.0001
Male	50.3	48.3	52.4	
Income Quintile				<0.0001
Q1	17.7	17.8	17.5	
Q2	19.8	20.0	19.6	
Q3	19.7	19.8	19.7	

Q4	20.8	20.6	21.1	
Q5	21.9	21.8	22.1	
Ethnic Concentration				0.39
Q1	21.0	21.0	21.0	
Q2	20.2	20.3	20.2	
Q3	19.4	19.3	19.5	
Q4	19.0	19.0	19.0	
Q5	20.3	20.3	20.3	
Place of Residence				<0.0001
Rural	13.9	13.5	14.3	
Type of Cancer				<0.0001
Breast	17.0	18.0	16.1	
Colon and rectum	12.6	12.1	13.1	
Digestive system except colon and rectum	4.7	4.3	5.1	
Female genital	6.8	6.7	6.8	
Lung and bronchus	6.4	6.2	6.7	
Prostate	18.5	19.3	17.7	
Others	18.7	17.5	19.9	
Haematological	8.8	9.0	8.6	
Urinary system	6.5	6.9	6.0	
Cancer Stage				<0.0001
I	16.9	17.8	16.0	
II	21.6	22.2	21.1	
III	10.8	10.0	11.6	
IV	6.7	5.6	7.8	
Unknown	44.0	44.4	43.5	
Number of Other Comorbidities				<0.0001
0	13.1	8.4	17.9	
1	23.2	19.7	26.8	
2	22.2	22.4	22.1	
3	16.5	18.6	14.4	
4+	25.0	30.9	18.8	
Death in the study period				<0.0001
Yes	37.8	36.8	38.8	

Table 2 shows the cumulative incidence of mood disorders, overall, and according to the patient's sociodemographic and clinical characteristics. The cumulative incidence of mood disorders in the study population was 16.9 (95% CI 16.6-17.3) per 1,000. Among those with

arthritis, 17.0 (95% CI 16.5-17.6) per 1000 and among the patients without arthritis 16.8 (95% CI 16.3-17.3) per 1,000 population developed mood disorders. The risk of mood disorders was higher with an increasing number of additional comorbidities, among younger patients, females, in lower socio-economic conditions, and rural residents. The patients with lung, hematological, and urinary system cancer had a higher incidence of mood disorders.

Table 2.

Crude incidence of mood disorders in cancer patients overall, by arthritis status and other characteristics

Characteristics		N with mood disorders	Cumulative incidence of mood disorders (per 1000 population) (95% CI)	p-Value
All population		7,526	16.9 (16.6-17.3)	N/A
Presence of arthritis prior to mood disorders				
	Yes	3,847	17.0 (16.5-17.6)	0.54
	No	3,679	16.8 (16.3-17.3)	
Age Group				
	18-44	962	21.3 (19.9-22.6)	<0.0001
	45-64	2,993	16.7 (16.1-17.3)	
	>=65	3,571	16.2 (15.7-16.8)	
Sex				
	Male	3,381	15.1 (14.6-15.6)	<0.0001
	Female	4,145	18.8 (18.2-19.3)	
Income Quintile				
	Q1	1,653	21.1 (20.1-22.2)	<0.0001
	Q2	1,567	17.9 (17.0-18.7)	
	Q3	1,441	16.5 (15.6-17.3)	
	Q4	1,388	15.0 (14.3-15.8)	
	Q5	1,446	14.9 (14.1-15.6)	
Ethnic Concentration				
	Q1	1,562	16.9 (16.1-17.8)	0.50
	Q2	1,491	16.8 (15.9-17.6)	
	Q3	1,444	16.9 (16.0-17.8)	
	Q4	1,453	17.4 (6.5-18.3)	
	Q5	1,455	16.3 (15.5-17.1)	

Place of Residence			
Rural	1,118	18.1 (17.1-19.2)	0.01
Urban	6,401	16.7 (16.3-17.1)	
Type of Cancer			
Breast	1,353	17.9 (16.9-18.8)	<0.0001
Colon and rectum	945	16.9 (15.8-18.0)	
Digestive system except colon and rectum	376	18.1 (16.3-19.9)	
Female genital	526	17.5 (16.0-19.0)	
Lung and bronchus	546	19.1 (17.5-20.7)	
Prostate	966	11.7 (11.0-12.5)	
Others	1,401	16.9 (16.0-18.7)	
Haematological	894	22.9 (21.4-24.4)	
Urinary system	519	18.0 (16.5-19.6)	
Cancer Stage			
I	1,180	15.7 (14.8-16.6)	<0.0001
II	1,331	13.8 (13.1-14.6)	
III	765	16.0 (14.8-17.1)	
IV	489	16.5 (15.0-17.9)	
Unknown	3,761	19.2 (18.6-19.9)	
Number of Other Comorbidities			
0	199	3.4 (2.9-3.9)	<0.0001
1	1,205	11.7 (11.0-12.4)	
2	1,449	14.7 (13.9-15.4)	
3	1,382	18.8 (17.8-19.8)	
4+	3,291	29.6 (28.6-30.6)	
Death during the study period			<0.0001
Yes	4,095	24.4 (23.6-25.1)	
No	3,431	12.4 (12.0-12.8)	

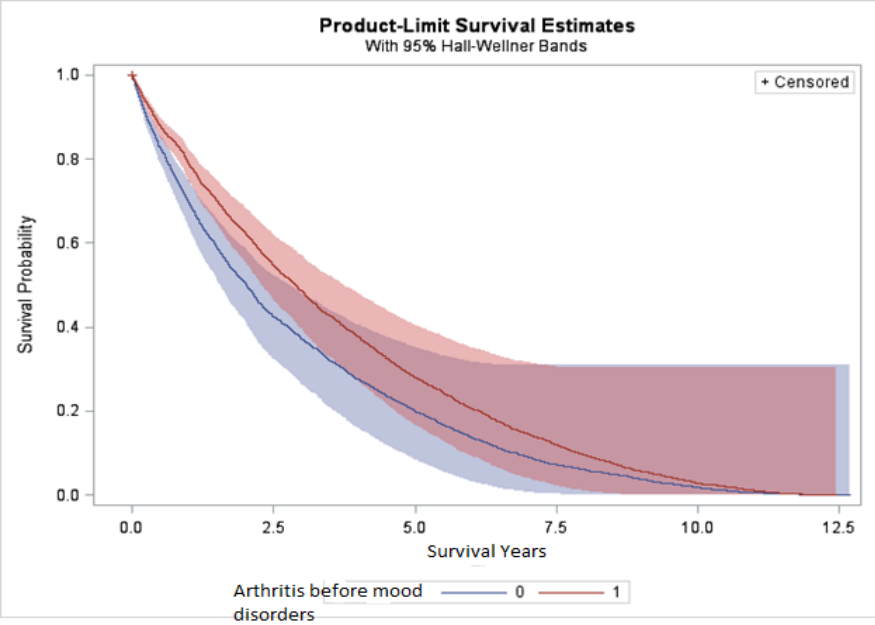
Crude Impact of Arthritis and MMB on the Time to the Development of Mood Disorders

The Kaplan Mayer (K-M) curve in figure 1 showed that the probability of developing mood disorders was significantly higher ($p<0.0001$) in cancer patients without arthritis compared to those with arthritis. The difference in the impact of arthritis on the development of mood disorders was substantial only 2 years after the initial cancer diagnosis (confidence intervals overlapped after 2 years). However, it should be noted that patients without arthritis were younger and had a higher prevalence of stage III or IV cancer (19.4% vs. 15.6%) than patients with arthritis. Both younger

age and stage III or IV cancer were associated with increased risk of mood disorders, which might explain the higher probability of developing mood disorders in patients without arthritis over time. However, the impact of arthritis on the development of mood disorders adjusted for age and stage of cancer will be tested in the Cox model.

On the other hand, the time to developing mood disorders was significantly shorter among patients without any other comorbidities and the time to mood disorders increased with the presence of additional comorbidities (results not shown). Perhaps, people with multiple comorbidities had misattribution of their depressive symptoms with the symptoms of other chronic conditions leading to significantly less likelihood of reporting mood disorders. Arthritis was associated with a lower probability of developing mood disorders in patients with cancer over time irrespective of the number of other co-occurring chronic conditions (appendix C).

Fig 1: Time to the development of mood disorders in cancer patients with or without arthritis



A multivariate Cox Proportional Hazard Model was then fitted to examine the adjusted impact of arthritis and MMB on the development of mood disorders in cancer patients. The covariates included in the multivariate analysis were tested for proportionality by using LLS (log of negative log of estimated survivor functions versus the log of time) curve and Schoenfeld residuals test. As a result, arthritis, multimorbidity, and age were included in the Cox hazard model as time-varying covariates, using interaction with the log of time. All the other covariates were proportional.

Adjusted Impact of Arthritis on the Development of Mood Disorders, Overall and by Cancer Types

Table 3.

Adjusted impact of arthritis on the development of mood disorders in cancer patients

Characteristics		Hazard Ratio	95% CI of HR
Arthritis (ref = no)	Yes	1.19	0.92-1.55
Arthritis*log(time)		0.97 (p=0.09)	
Age		1.49	1.48-1.51
Age*log (time)		0.94 (p<0.0001)	
Sex (ref = male)	Female	0.92	0.87-0.97
Rural (ref = no)	Yes	0.95	0.88-1.02
Income Quintile (ref = Q5)	Q1	0.98	0.91-1.06
	Q2	0.97	0.90-1.04
	Q3	0.99	0.93-1.07
	Q4	0.98	0.91-1.05
Ethnic Concentration Quintile (ref = Q5)	Q1	1.08	1.00-1.17
	Q2	1.06	0.98-1.14
	Q3	1.06	0.98-1.15
	Q4	1.07	0.99-1.15

Characteristics		Hazard Ratio	95% CI of HR
Cancer Types (ref = others)	Breast	1.14	1.05-1.24
	Colon and rectum	1.11	1.01-1.21
	Digestive system except colon and rectum	1.19	1.06-1.34
	Female genital	1.18	1.06-1.32
	Hematological	1.02	0.93-1.11
	Lung and bronchus	1.26	1.14-1.40
	Prostate	1.15	1.04-1.26
	Urinary system	1.09	0.98-1.21
Presence of other comorbid conditions (ref = no other conditions)	1 other condition	1.67	1.35-2.08
	2 other conditions	4.46	3.14-6.33
	3 other conditions	10.85	6.63-17.74
	4 or more other conditions	21.51	11.50-40.22
MMB level*log (time)		0.89 ($p < 0.0001$)	
Cancer stage (ref =I)	II	1.05	0.97-1.14
	III	1.06	0.98-1.18
	IV	1.18	1.08-1.35
	Unknown	1.00	0.94-1.08
Death during the study period (ref = no)	Yes	1.08	1.02-1.15

After adjusting for age, sex, residence, income, ethnicity, cancer types, stage, and the number of other comorbid conditions, arthritis did not remain significantly associated with an increased risk of mood disorders in cancer patients. The association did not vary according to time either. The adjusted impact of arthritis also did not vary according to MMB level (interaction not

significant, results not shown). MMB was associated with the risk of mood disorders, and its impact decreased with time. Other significant risk factors for developing mood disorders were increasing age, male sex, certain cancer types, stage IV cancer, and death within the study period. Cancer patients who died at any point during the study period had a higher probability of developing mood disorders than those who were still alive.

We looked at the impact of different types of arthritis (osteoarthritis and rheumatoid arthritis) on the development of mood disorders. There was no impact of osteoarthritis and rheumatoid arthritis on the risk of mood disorders at baseline and over time. Then we performed stratified analyses by cancer types to determine whether the impact of arthritis and MMB on the development of mood disorders varied by the clinical aspects of cancer. Cancer types are clinically different and may impact differently care management or patient outcomes including the risk of mood disorders, hence, the relevance to stratify. Arthritis was associated with the highest risk of mood disorders at baseline among patients with lung (HR 5.73; CI 1.85-17.75), prostate (HR 4.12; CI 1.49-11.33), and urinary system (HR 6.16; CI 1.95-19.44) cancers. The risk of mood disorders decreased significantly with time among all the three above-mentioned cancer groups. On the other hand, the baseline risk of mood disorders was lowest among breast cancer patients with arthritis (HR 0.45; CI 0.21-0.99) which did not vary over time (Table 4). Nevertheless, among the patients with colon and other digestive systems, female genital or hematological cancer, arthritis was not linked significantly with the development of mood disorders.

Table 4.

Adjusted Impact of arthritis on the development of mood disorders stratified by cancer types

Cancer Type	Description	Hazard ratio	95% Confidence interval	
Breast	Arthritis Yes vs No	0.45	0.21	0.99

	Arthritis* log (time)	1.10 (p=0.11)		
Colon and rectum	Arthritis Yes vs No	0.50	0.24	1.05
	Arthritis* log (time)	1.10 (p=0.08)		
Digestive system except	Arthritis Yes vs No	0.92	0.24	3.51
colon and rectum	Arthritis* log (time)	0.99 (p=0.94)		
Female genital	Arthritis Yes vs No	1.01	0.28	3.68
	Arthritis* log (time)	1.00 (p=0.99)		
Hematological	Arthritis Yes vs No	0.98	0.45	2.14
	Arthritis* log (time)	0.99 (p=0.79)		
Lung and bronchus	Arthritis Yes vs No	5.73	1.85	17.75
	Arthritis* log (time)	0.77 (p=0.003)		
Prostate	Arthritis Yes vs No	4.12	1.49	11.33
	Arthritis* log (time)	0.81 (p=0.003)		
Urinary system	Arthritis Yes vs No	6.16	1.95	19.44
	Arthritis* log (time)	0.77 (p=0.003)		

*****Adjusted for age, sex, residence, income, ethnic concentration, cancer stage, MMB level, and death during the study period.

Sensitivity Analysis

A sensitivity analysis was performed among patients who survived less than a year after the cancer diagnosis (N = 144,207) to explore whether arthritis and MMB had similar effects on the development of mood disorders in this group of patients. These patients were older (mean age 72.8 years), more likely to be male, be diagnosed with lung cancer, and only 40% had arthritis prior to mood disorders (Appendix E). The cumulative incidence of mood disorders was lower, 7.1 per 1,000 population, and slightly but not statistically different between patients with arthritis (7.5 per 1,000), and those without arthritis (6.8 per 1,000). In the multivariate Cox model, arthritis and MMB did not have a significant association with mood disorders (Appendix F).

Discussion

This study examined the impact of arthritis on the development of mood disorders in cancer patients considering the role of other comorbid conditions. The findings showed that arthritis was not associated with the risk and time to development of mood disorders.

We found an overall incidence of mood disorders of 16.9 per 1000 among cancer patients, which is consistent with previous population-based studies (Hung et al., 2013; Zhu et al., 2017). The study by Zhu et al. (2017) was among the Swedish cancer patients who are comparable to the Canadian population according to the sociodemographic characteristics. Zhu et al. (2017) found that the incidence of mood disorders including depression was 13.9 per 1,000 population (J. Zhu et al., 2017). However, they only considered major depressive disorders which might explain the relatively lower incidence found in their study.

Our study showed that arthritis was not associated with an increased risk of mood disorders in cancer patients. Several studies have focused on the association between arthritis and mood disorders in the general population, but no study have addressed this issue among cancer patients specifically. As opposed to our findings, all these studies showed that arthritis was associated with increased risk of mood disorders (He et al., 2008; Hsu et al., 2014; Husaini & Moore, 1990; Jeong et al., 2017; Stubbs et al., 2016). He et al. (2008) found 1.9 times higher odds of mood disorders in patients with arthritis compared to those without arthritis (He et al., 2008). Stubbs and colleagues (2016) found a 17% higher risk of depression among osteoarthritis patients (Stubbs et al., 2016). Both cancer and arthritis are characterized by pain which is a significant predictor of depression (Alemayehu et al., 2018). So, we expected a higher association between arthritis and mood disorders in cancer patients. However, this hypothesis was not confirmed. The K-M curve showed that arthritis was associated with decreased risk of mood disorders up to two years after cancer

diagnosis and the impact of arthritis on the risk of mood disorders later subsided. In the Cox model, after adjusting for covariates, arthritis showed no association with mood disorders in cancer patients. Perhaps, the uncontrolled pain associated with arthritis could obfuscate mood disorder symptoms leading to ignoring and under-reporting the psychological condition in cancer patients with arthritis. Besides, the severity of certain cancers could predispose the patients to develop mood disorders masking the impact of arthritis.

While the specific condition arthritis was not a risk factor, our study found the number of other comorbidities was associated with an increased risk of developing mood disorders both among the cancer patients with and without arthritis. Patients with four or more additional conditions had around 21 times higher risk of mood disorders at baseline compared to those without other chronic conditions but the risk decreased over time. This finding is consistent with the previous literature (Rice et al., 2018; Zoorob et al., 2019). However, the above-mentioned studies did not consider the impact of MMB over time and our study showed that the risk of mood disorders associated with MMB decreased over time. Complex cancer patients suffering from MMB for a longer period could ignore psychological conditions due to the severity of other conditions which might lead to the diminished impact of MMB on mood disorders later after their cancer diagnosis.

Other risk factors included were increasing age and male sex. The increased risk of mood disorders related to male sex found in our study is contrary to previous studies where female sex had been described as a risk factor for developing mood disorders (Walker et al., 2014). In our study, the crude incidence of mood disorders was higher among the females but after adjusting for the covariates, male sex became a significant risk factor for mood disorders. Male patients were older, had a higher number of comorbidities. Elderly patients were more likely to develop late-stage cancer and had MMB. Both MMB and stage III and IV cancers are proven risk factors for

mood disorders (Zoorob et al., 2019; Walker et al., 2014), and this might explain the increased risk of mood disorders associated with age and among the males when adjusted for the confounders like cancer stage and number of other chronic conditions.

When looking at the association between arthritis and mood disorders within cancer types we found that the impact of arthritis on the risk of mood disorders was highest at the baseline among lung cancer patients. In these patients, with the advancement of cancer, the severity of the disease and related complications might be responsible for causing depression. As a result, the impact of arthritis on the development of mood disorders was diluted over time in lung cancer patients. On the contrary, breast cancer patients had a lower baseline risk of mood disorders when they had arthritis, but the impact of arthritis increased over time. Generally, breast cancer patients had better survival, and many of them suffered from arthritis for a longer period. There are common drugs used to treat arthritis and cancer, for example, steroid has been linked to increased risk of depression (Caruso et al., 2017). As a result, the impact of arthritis on the risk of mood disorders could increase from the baseline risk later after a cancer diagnosis.

Strengths and Limitations

The cases of mood disorders were diagnosed using ICD-10 codes in hospitalization or physician's claim data and ICD-9 code in OHIP, DAD, and NACRS. The OHIP database contains ICD-9 codes 296 (Major Depression/ Bipolar disorder), 300 (Anxiety neurosis, hysteria, neurasthenia, obsessive-compulsive neurosis, reactive depression), and 311 (Depressive Disorder NOS) for classifying mood disorders. In DAD and NACRS, mood disorders are classified using ICD-10 codes F30-34, F38-39 (Grigoriadis et al., 2017). We included ICD 10 codes F30-34, F38-39 in DAD or NACRS but ICD-9 code 296 only from OHIP and did not consider 300 and 311 to identify cases of mood disorders. However, linking the databases to include the patients of mood

disorders from both hospitalizations and physician claim data enabled us to get a precise estimate of the incidence of mood disorders. Moreover, ICD 9 codes 300 and 311 is not specific for depression; hence they were not considered to diagnose the cases of mood disorders.

The study was conducted with the administrative health databases and included only those cancer patients having contact with the health care system. However, all the adult cancer patients diagnosed between 2003-2013 were considered in the study and despite the limitation of including only those having contact with the health care system, the overall coverage was good. Cancer patients who died within their first year of diagnosis were not considered in the study leading to potential selection bias. A sensitivity analysis was conducted to examine the role of arthritis and MMB in developing mood disorders among cancer patients who survived less than a year. The findings showed that arthritis had similarly no effect on the development of mood disorders among these cancer patients. In contrast to the patients surviving greater than a year, MMB was also not linked to the development of mood disorders in cancer patients surviving less than a year. Hence, it is more relevant to address MMB including arthritis in cancer patients who survived longer to improve their psychological outcomes.

There might be a misclassification bias while reporting arthritis and mood disorders by either patients or physicians. Administrative data, for example, DAD has 85% accuracy for diagnostic code (Juurlink et al., 2006). We probably underestimated the incidence of mood disorders due to the misclassification introduced by using administrative data. Moreover, the definition used in this study to identify the cases of osteoarthritis from administrative databases showed lower sensisitivity while having higher specificity (Shrestha et al., 2016). So, there might be under estimation of the prevalence of arthritis diluting its effect on the development of mood disorders in cancer patients. Furthermore, many comorbid conditions occurred after the diagnosis of mood

disorders. So, there was chance of an error in counting the number of comorbid conditions, causing misclassification. We considered 16 selected chronic conditions due to their population prevalence and associated costs. There are other severe chronic conditions, for example, congenital anomalies, thyroid problems, glaucoma, or chronic skin diseases that may be relevant but not included in the study. Besides, while observing the impact of MMB, we only counted the number of chronic conditions without contemplating their severity and time of occurrence.

Despite the limitations**,** the study had many strengths in terms of data used, study design, and analytical approach. It was a population-based retrospective cohort study including all adults in Ontario diagnosed with cancer between 2003 and 2013 and without preexisting mood disorders. The sample size was large and the follow-up period was between 5 to 15 years, allowing us to achieve a long-term estimate of the incidence of mood disorders in cancer patients at the population level. We detected mood disorders, arthritis, and other chronic conditions from various Canadian administrative databases. Moreover, ICES databases are evidence-based and extensively used in the similar literature on MMB (Griffith et al., 2019; Gruneir et al., 2016; Koné Pefoyo et al., 2015; Moin et al., 2018; Mondor et al., 2017, 2018; Ryan et al., 2018).

Conclusion

The study revealed that arthritis did not increase the risk of mood disorders, instead, MMB is associated with the occurrence of mood disorders in cancer patients. The association between arthritis and mood disorders was similar over the study period indicating that arthritis did not increase the risk of mood disorders at any point in time in cancer patients. On the other hand, the risk of mood disorders increased with the number of chronic conditions at baseline but the impact of MMB decreased with the advancement of cancer. The study also provided insight into other sociodemographic and clinical factors increasing the risk of depression in cancer patients.

Mood disorders impact cancer outcomes including survival, quality of life, cancer management, and health care utilization (Iglay et al., 2017; Mehta & Roth, 2015; Villarreal-Garza et al., 2019). Cancer patients with psychological conditions have lower survival and the management of cancer becomes complicated in the presence of mood disorders. We found that mood disorders were more prevalent among male cancer patients, patients with lung and digestive system cancer in advanced-stage cancer. This study provides evidence for addressing multimorbidity to decrease the incidence of comorbid psychiatric disorders in cancer patients. To ensure proper care management in cancer patients, the disease clusters highly responsible for developing mood disorders should be identified and treated early. Future research can be done to detect the disease clusters within each MMB level associated with the highest risk of mood disorders. Identifying cancer patients most susceptible to developing mood disorders may contribute to better outcomes and targeted person-centered care.

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Appendices

Appendix A: Administrative Databases Used in the Study and Corresponding Variables

Database	Description	Variables
Registered Persons Database (RPDB)	Includes data on all person eligible for the Ontario Provincial Health care program and provides demographic information like age, sex, date of birth, death, residence, and neighborhood income	Age, sex, residence, income quintile
Discharge Abstract Database (DAD)	Hospital inpatient data. It includes data on hospital admission, discharge, length of stay, primary diagnosis, other diagnoses, procedures, and interventions	Arthritis, mood disorders, and other comorbidities using the ICD codes, date/year of diagnosis
Ontario Health Insurance Plan (OHIP) claims	Physician's claim database. Includes the date of visit, diagnosis, procedures such as laboratory tests and vaccination	Arthritis, mood disorders, and other comorbidities using the ICD codes, date/year of diagnosis
National Ambulatory Care Reporting System (NACRS)	Includes hospital outpatient data, diagnosis, day surgeries, and Emergency department visits	Arthritis, mood disorders, and other comorbidities using the ICD codes, date/year of diagnosis

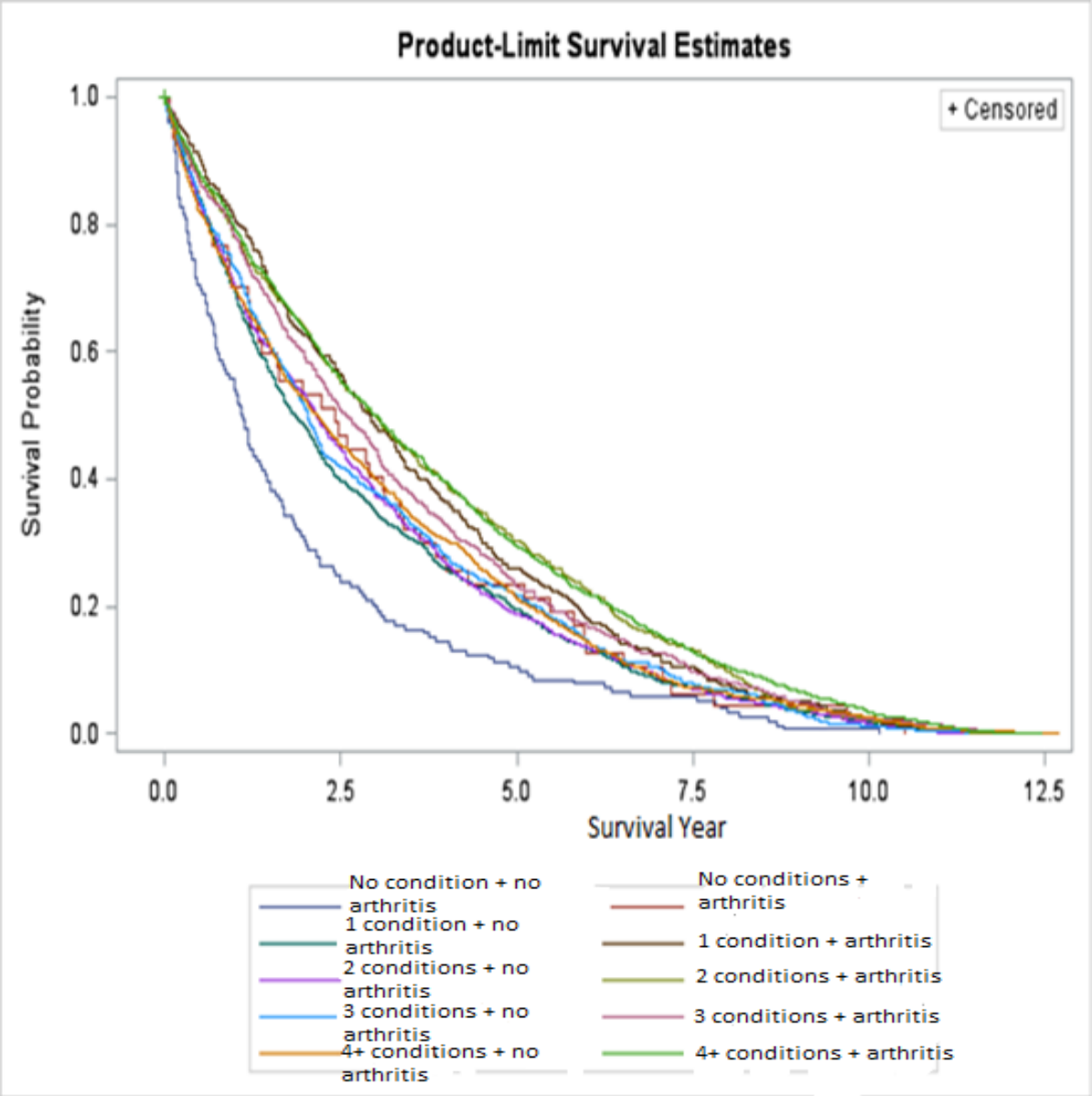
Ontario Cancer Registry (OCR)	Provincial database of all the residents of Ontario having a diagnosis of cancer. Contains demographic and clinical information including the date of diagnosis, primary cancer site, cancer stage, and death	Age, sex, date of birth, death, cancer type, date of cancer diagnosis
Ontario Marginalization Index (ON-Marg)	It is a measure of inequalities between the geographical areas based on four dimensions; residential instability, material deprivation, ethnic concentration, and dependency	Ethnic concentration Quintile

Appendix B: ICD codes for chronic conditions

Condition	ICD 9 / OHIP	ICD 10
AMI	410	I21, I22
Arthritis - Osteoarthritis	715	M15-M19
Arthritis - Other Arthritis (Synovitis, Fibrositis, Connective tissue disorders, Ankylosing spondylitis, Gout Traumatic arthritis, pyogenic arthritis, Joint derangement, Dupuytren's contracture, Other MSK disorders)	727, 729, 710, 720, 274, 716, 711, 718, 728, 739	M00-M03, M07, M10, M11-M14, M20-M25, M30-M36, M65-M79
Arthritis - Rheumatoid arthritis		M05-M06
Asthma	493	J45
Cancer	140-239	C00-C26, C30-C44, C45-C97
Cardiac Arrythmia	427.3 (DAD) / 427 (OHIP)	I48.0, I48.1
CHF	428	I500, I501, I509
COPD	491, 492, 496	J41, J43, J44
Dementia	290, 331, 797 (OHIP) / 290.0, 290.1, 290.3, 290.4, 290.8, 290.9, 294.1, 294.8, 294.9,	F000, F001, F002, F009, F010, F011, F012, F013, F018, F019, F020, F021,

	331.0, 331.1, 331.2, 797 (DAD)	F022, F023, F024, F028, F03, F051, F065, F066, F068, F069, F09, G300, G301, G308, G309, G310, G311, R54
Mood Disorders	296	F30-F34, F38, F39
Diabetes	250	E08 - E13
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15
Osteoporosis	733	M81 M82
Renal failure	403, 404, 584, 585, 586, v451	N17, N18, N19, T82.4, Z49.2, Z99.2
Stroke	430, 431, 432, 434, 436	I60-I64
Coronary syndrome (excluding MI)	411-414	I20, I22-I25
Other mental disorders (substance use disorder, psychotic disorder, anxiety, stress reaction-specifically PTSD, personality disorder)	291, 292, 303, 304, 305, 295, 298, 297, 300, 308, 301	F10-F19, F55, F20-F29, F40-F42, F93, F43, F60

Appendix C: K-M Curve Representing the Impact of Arthritis on the Time to the Development of Mood Disorders Considering the Level of Multimorbidity



Appendix D: Adjusted Impact of Arthritis on the Development of Mood Disorders at Different MMB Level

Description	Point Estimate	95% Wald Confidence Limits	
No other comorbidities (arthritis yes vs no)	0.92	0.59	1.43
1 other condition (arthritis yes vs no)	1.07	0.77	1.49
2 other conditions (arthritis yes vs no)	1.05	0.77	1.43
3 other conditions (arthritis yes vs no)	1.15	0.85	1.55
4 or more other conditions (arthritis yes vs no)	1.14	0.87	1.50
Arthritis*log(time)	0.98 (p=0.29)		

Appendix E: Characteristics of Cancer Patients by the length of survival (Less than a Year vs More than a Year)

Characteristics	All the Cancer patients N = 588759 (%)	Patients surviving more than a year N=444,552 (%)	Patients surviving less than a year N=144,207 (%)
Development of mood disorders			
Yes	1.4	1.7	0.7
Arthritis prior to mood disorders			
Yes	48.1	50.8	39.7
Age at cancer diagnosis (years)			
Mean (SD)	65.6 ± 14.4	63.2 ± 14.2	72.8 ± 12.6
Range (min-max)	18-103	18-103	18-103
Sex			
Male	51.2	50.3	54.1
Income Quintile			
Q1	18.9	17.7	22.7
Q2	20.3	19.8	21.8
Q3	19.7	19.7	19.6
Q4	20.3	20.8	18.6
Q5	20.8	21.9	17.1
Ethnic Concentration			
Q1	21.7	21.0	23.7
Q2	20.6	20.2	21.9
Q3	19.4	19.4	19.1
Q4	18.7	19.0	17.9
Q5	19.6	20.3	17.3
Place of Residence			
Rural	14.3	13.9	15.4
Type of Cancer			
Breast	13.5	17.0	2.8
Colon and rectum	12.0	12.6	10.0
Digestive system except colon and rectum	8.2	4.7	19.2
Female genital	6.0	6.8	3.7
Lung and bronchus	12.5	6.4	31.2
Prostate	14.6	18.5	2.7
Others	18.0	18.7	15.9
Haematological	9.0	8.8	9.5
Urinary system	6.1	6.5	5.1
Cancer Stage			

	I	13.3	16.9	2.1
	II	17.2	21.6	3.6
	III	10.2	10.8	8.3
	IV	11.6	6.7	26.7
	Unknown	47.7	44.0	59.3
Number of Other Comorbidities				
	0	12.7	13.1	11.6
	1	22.3	23.2	19.7
	2	22.1	22.2	21.7
	3	16.9	16.5	18.0
	4+	26.0	25.0	29.1

Appendix F: Adjusted Impact of Arthritis on the Development of Mood Disorders among Cancer Patients Surviving Less than a Year

Characteristics		p-value	Hazard Ratio	95% CI of HR
Arthritis (ref = no)	Yes	0.52	0.96	0.84-1.09
Age		0.04	1.006	1.00-1.01
Sex (ref = male)	Female	0.05	1.14	0.99-1.30
Rural (ref = no)	Yes	0.84	1.14	0.99-1.30
Income Quintile (ref = Q5)	Q1	0.84	1.02	0.83-1.25
	Q2	0.94	0.99	0.81-1.21
	Q3	0.43	0.92	0.75-1.13
	Q4	0.84	0.98	0.79-1.21
Ethnic Concentration Quintile (ref = Q5)	Q1	0.85	1.02	0.82-1.27
	Q2	0.86	1.02	0.83-1.25
	Q3	0.22	0.88	0.71-1.08
	Q4	0.23	0.88	0.72-1.08
Cancer Types (ref = others)	Breast	0.78	0.94	0.63-1.41
	Colon and rectum	0.48	0.91	0.71-1.17
	Digestive system except colon and rectum	0.72	0.96	0.78-1.19
	Female genital	0.84	1.04	0.71-1.51
	Hematological	0.65	0.95	0.74-1.20
	Lung and bronchus	0.58	0.94	0.76-1.16
	Prostate	0.02	0.63	0.43-0.94
	Urinary system	0.09	0.79	0.60-1.03
Presence of other comorbid conditions	1 other condition	0.05	1.32	1.00-1.73
	2 other conditions	0.20	1.19	0.90-1.56

Characteristics		p-value	Hazard Ratio	95% CI of HR
(ref = no other conditions)	3 other conditions	0.07	1.29	0.97-1.71
	4 or more other conditions	0.33	1.14	0.87-1.50
Cancer stage (ref = I)	II	0.46	1.17	0.77-1.79
	III	0.47	1.15	0.78-1.70
	IV	0.07	1.39	0.97-2.00
	Unknown	0.01	1.55	1.09-2.22

Chapter 5: Impact of Mood Disorders and Arthritis on the Health Care Utilization of Cancer Patients

Abstract

Background: Mood disorders and arthritis are common in cancer patients and impact their outcomes. Because cancer patients often have multiple conditions, this may exacerbate the effect of mood disorders and arthritis on their use of health services. This study will evaluate the impact of mood disorders and arthritis on health care utilization (HCU) among cancer patients and how it may differ with additional comorbidities.

Method: A retrospective cohort study using health administrative data was conducted. The study population included those who were diagnosed with cancer between April 1, 2003, and March 31, 2013, and survived at least a year thereafter. They were followed up till 31st March 2018 to identify the occurrence of arthritis and mood disorders as well as to measure their health care utilization (HCU) following a cancer diagnosis. A negative binomial model was fitted to assess the adjusted impact of mood disorders, arthritis, and comorbidities on the health care utilization of cancer patients in terms of hospitalizations and emergency visits.

Results: The study population included 453,012 participants. Among the cancer patients, 51.03% had a diagnosis of arthritis and 3.52% had mood disorders. Compared to patients without mood disorders (0.57 ± 0.92), those with mood disorders before (0.73± 1.06) and after (1.09 ± 1.33) cancer had on average a higher number of hospitalizations per person-year. The average ED visits per person-year were also higher in patients with mood disorders before (1.03 ± 1.68) and after (1.20 ± 2.10) cancer compared to those without any mood disorders (0.66 ± 1.25). Arthritis was associated with increased ED visits and hospitalizations if diagnosed before cancer but decreased hospitalizations and ED visits if diagnosed after cancer. In the multivariate regression model, the combined presence of arthritis and mood disorders before and after cancer was associated with a 25% (95% CI = 20-29%) and 28% (95% CI = 20-37%) higher risk of hospitalization, respectively.

Furthermore, the co-occurrence of arthritis and mood disorders had been linked to 75% (95% CI = 69-81%) and 60% (95% CI = 50-69%) increased risk of ED visits when both the conditions were diagnosed before and after cancer, respectively. The presence of other comorbidities increased HCU in cancer patients.

Significance and Policy Implication: The findings confirm that mood disorders and arthritis are important predictors of HCU. Addressing the health care needs of patients with multimorbidity, especially mood disorders, and identifying other co-occurring conditions responsible for higher utilization of health services will ensure optimum patient care and decrease the burden on the health care system.

Introduction

Cancer patients represent the highest users of the health care system. Cancer patients with multimorbidity (MMB) (i.e. complex cancer patients) have, on average, 6.8 primary care visits, and 9.7 specialists' visits per month (ICES, 2014). Several factors, such as sociocultural, sociodemographic, social-psychological, organizational, and social systems have been shown to contribute to health care utilization (HCU) (Anderson, 1973). For example, Johansson and colleagues (2004) found that cancer type, stage, age, comorbidities, functional status, pain, lower socioeconomic condition, and survival were all related to HCU among cancer patients (Johansson et al., 2004)

Cancer patients often have co-occurring chronic conditions, and arthritis and mood disorders are among the most common comorbidities in cancer patients (Hartung et al., 2017a; Koné Pefoyo et al., 2015; Ng et al., 2018). Both arthritis and mood disorders had been individually linked to increased utilization of the health care system (Aubert et al., 2019; Guo et al., 2008; Robinson et al., 2016; Wright et al., 2010). Mood disorders including major depressive disorder (MDD) were responsible for a higher number of hospital admissions, health care professional visits, and longer hospital stays (Patel et al., 2015; Patten & Beck, 2004). Similarly, multimorbidity (MMB) increases HCU in patients with depression, and in the opposite direction, depression increases the complexity of multimorbid disease management (Bock et al., 2014; Robinson et al., 2016).

Arthritis is also associated with increased HCU both among patients with or without cancer (Wright et al., 2010; Jacobi et al., 2001). Patients with osteoarthritis have more annual emergency visits, hospitalizations, and physician visits compared to those without osteoarthritis, and their HCU is greater with the presence of comorbidities like cardiovascular disease, diabetes, psychiatric disorder, and cancer (Wright et al., 2010). In patients with rheumatoid arthritis, 97%

had at least one specialist visit, and their use of health services increased with the presence of two or more chronic conditions including cardiovascular, respiratory diseases, cancer, and depression (Jacobi et al., 2001).

Research evidence shows that cancer, arthritis, and mood disorders significantly increase HCU. However, their combined effect is unknown. The objective of this study is to reveal the combined impact of arthritis and mood disorders on the HCU of cancer patients considering the presence of other comorbid conditions.

Methods

Study Design and Study Population

A retrospective cohort study with health administrative data was conducted to examine the impact of arthritis and mood disorders on the HCU of cancer patients in Ontario, Canada. The study included all adult patients (18 years or more) with a valid health card, diagnosed with cancer in Ontario between April 1, 2003, and March 31, 2013, and who survived at least one year after their initial cancer diagnosis. The patients who survived less than a year after their cancer diagnosis were excluded to minimize reverse causality because a higher encounter with the health care system due to their disease severity might be related to the development of depression or arthritis among them. We assessed the occurrence of arthritis, mood disorders from 2003 and the HCU following cancer diagnosis in terms of hospitalizations and ED visits until March 2018 or death.

Data Sources

This study was based on provincial administrative databases in Ontario housed at the Institute for Clinical Evaluative Sciences (ICES) that were linked to define the study population and outcome of interest. ICES is a research organization and the databases contain information on

health services utilization, disease registries, and basic population characteristics. All the Ontario residents including immigrants are covered by provincial health insurance and are assigned a unique health card number. ICES members access, link, and analyze health administrative data using this unique identifier (Ishiguro et al., 2016). The specific databases used for this study include the Ontario Cancer Registry (OCR), Ontario Health Insurance Plan (OHIP), Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), and the Registered Person Database (RPDB). The details of the databases are described in Appendix A. The ethics approval for this study was obtained from ICES and Lakehead University Research Ethics Board.

Study Measures

The primary exposure was the presence of mood disorders (yes/no) and arthritis (yes/no). Mood disorders and arthritis (both osteoarthritis and rheumatoid arthritis) were identified using specific ICD-10 codes in DAD as well as ICD-9 codes in OHIP, DAD, and NACRS (Appendix B). Patients who have at least two claims with mood disorders or arthritis in OHIP in any consecutive two years or one registration in DAD or NACRS within a year were considered as having arthritis or mood disorders. There is evidence that if cases of depression were diagnosed using the case definition used in this study, the sensitivity of DAD and OHIP database is 75% and specificity is 93% for diagnosing depression (Fiest et al., 2014). For identifying patients with arthritis, the administrative databases also had good validity (Rahman et al., 2016; Widdifield et al., 2014). Arthritis and mood disorders were measured throughout the study period (2003-18) and may have been present at the time of cancer diagnosis. The exposure was defined as mood disorders only before cancer, mood disorders only after cancer, arthritis only before cancer, arthritis only after cancer, both the conditions before cancer, both conditions after cancer, mood disorders

before/arthritis after cancer, and arthritis before/mood disorders after cancer. Besides cancer, arthritis, and mood disorders, other chronic conditions included in the study were acute myocardial infarction (AMI), asthma, cardiac arrhythmia, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), chronic coronary syndrome, dementia, diabetes, hypertension (HTN), other mental illnesses, osteoporosis, renal failure, and stroke as used in previous research on MMB (Koné Pefoyo et al., 2015). These conditions were categorized as no additional conditions, 1, 2, 3, and 4 or more additional conditions.

HCU between April 1, 2003, and March 31, 2018, represented the outcome of interest and included the cumulative number of hospital admissions and ED visits since cancer diagnosis. Patients were diagnosed at different times between 2003 and 2013 and may have died during follow-up; as such, we calculated the average number of hospitalizations and ED visits accounting for person-years (hospitalizations and ED visits per person-year). The other covariates included in the study were age, sex, ethnicity, place of residence, income quintile, cancer types, and stage which were selected as these factors may impact HCU in cancer patients (Hartung et al., 2017; Mausbach & Irwin, 2017; Nikbakhsh et al., 2014; Pitman et al., 2018; Yadav et al., 2019). Information on age and sex was derived from the Ontario Cancer Registry (OCR). Ethnic concentration quintiles were obtained from the Ontario Marginalization Index (ON-Marg) data where Q1 demonstrated the lowest ethnically concentrated and Q5 is the highest ethnically concentrated area (Matheson et al., 2012). The place of residence (rural/urban) and the neighborhood income quintiles were derived from RPDB. Neighborhood income quintiles are based on census data; quintile 1 (Q1) has the lowest income whereas quintile 5 (Q5) has the highest (Specifications, n.d.). Cancer sites and stages were obtained from the Ontario Cancer Registry

(OCR) and types were grouped using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) coding system (National Cancer Institute, 2008).

Analysis

All the statistical analyses were performed using SAS software (SAS Institute, n.d.). The relationships between arthritis, mood disorders, multimorbidity, and hospitalizations and ED visits per person-year were assessed with t-test and ANOVA. Considering that the dependent variables (number of hospitalizations and ED visits) were count data, and as the mean and variance were unequal, a negative binomial model was fitted to assess the adjusted impact of mood disorders and arthritis on the HCU rate among cancer patients. The model was adjusted for sociodemographic characteristics, level of multimorbidity, and cancer type and stages. The model was also tested including an interaction term between arthritis/mood disorders and the level of multimorbidity to identify significant interaction. The association between arthritis, mood disorders, and HCU was then analyzed within levels of multimorbidity (MMB) to test if MMB has a modifying effect (effect modification).

Results

The sample was comprised of 453,012 adult patients with cancer who were diagnosed between 2003-13 and survived one year or more after their cancer diagnosis. The average age of the study population was 63 years. In the study population, 3.52% had a diagnosis of mood disorders and 51.03% had arthritis. The proportion of cancer patients diagnosed with mood disorders before and after cancer was almost similar, whereas 71.8% of the cancer patients with arthritis received the diagnosis of arthritis before cancer. Among the patients who developed mood disorders after their cancer diagnosis, the mean time to mood disorders was 3.23 years with a median value of 2.41

years. The mean duration of follow up for these patients was 10.39 years and the mean time to death for those who died was 5.26 years (Appendix C)

On the other hand, in the patients who developed arthritis after cancer, the mean duration until the development of arthritis was 3.43 years. The average follow-up time for these patients was 10.83 years and the mean time to death was 6.69 years (Appendix C). Though mood disorders and arthritis after cancer diagnosis was considered as exposure irrespective of their time of occurrence, the mean time to diagnosis provides an idea about their time of occurrence and insight about whether they contributed to the utilization of health services. As the mean time to the development of arthritis and mood disorders were much lower than the mean follow-up time or time to death, it is expected that these conditions had probably contributed towards their health care utilizations. Moreover, we counted hospitalizations and ED visits after cancer diagnosis till 2018 or death. Then we calculated average annual hospitalizations and ED visits per person-year. So, if arthritis or mood disorders were diagnosed after initial contact with the health care system, these conditions would have impact on the subsequent use of health services by cancer patients.

Most of the patients with arthritis and mood disorders were older, predominantly female, more likely to have breast and prostate cancer, and had a higher number of other co-occurring conditions compared to those without arthritis and mood disorders (Table 1).

Table 1.

Study population characteristics according to the exposure status

Characteristics	Total N= 453,012	No arthritis/ mood	Mood disorders only		Arthritis only		Both the conditions		Mood disorders before and	Arthritis before and mood
			Before	After cancer	Before	After Cancer	Before	After Cancer		

		disorders N = 215,176	Cancer N = 3,513	N= 3,148	Cancer N = 163,325	N= 58,525	cancer N= 4,018	N= 1,302	arthritis after cancer N=929	disorders after cancer N= 3076
Age Group										
18-44	10.2	14.5	15.3	17.7	4.5	9.8	6.0	16.1	13.3	6.4
45-64	40.5	42.5	49.5	40.6	36.0	44.8	48.1	42.9	56.9	37.6
>65	49.3	43.1	35.3	41.7	59.5	45.5	45.8	41.0	29.7	56.0
Sex										
Male	50.1	52.5	43.8	48.9	47.7	50.3	36.4	41.4	34.7	42.4
Income Quintile										
Q1	17.8	17.4	25.0	22.8	18.1	16.8	25.4	22.6	24.1	21.1
Q2	19.8	19.6	22.0	21.2	20.1	19.4	20.9	20.6	19.9	20.8
Q3	19.7	19.7	18.2	18.8	19.9	19.6	18.8	19.3	18.3	19.6
Q4	20.8	21.1	17.3	18.2	20.5	21.0	17.4	18.6	18.5	18.8
Q5	21.9	22.2	17.6	19.0	21.3	23.1	17.3	18.8	19.1	19.8
Ethnic concentration										
Q1	21.0	21.0	20.0	21.6	21.1	20.7	18.4	19.8	18.5	21.1
Q2	20.2	20.2	19.0	19.9	20.5	19.7	20.0	20.6	17.3	20.1
Q3	19.4	19.5	19.9	19.6	19.3	19.4	19.6	18.6	21.4	19.8
Q4	19.0	18.9	21.3	19.3	18.9	19.2	20.9	19.8	23.1	19.8
Q5	20.3	20.3	19.7	19.5	20.1	21.0	21.1	21.2	19.6	19.1
Residence										
Rural	13.9	14.3	12.3	15.5	13.6	13.2	12.6	14.1	12.1	14.5
Type of Cancer										
Breast	17.1	16.0	18.2	15.7	17.5	19.3	20.3	21.7	26.8	18.8
Colon and rectum	12.6	13.1	11.8	13.2	12.1	12.1	10.8	11.7	9.3	12.2
Digestive system except colon and rectum	4.7	5.1	5.0	5.6	4.7	2.9	5.4	4.4	3.7	4.6
Female genital	6.8	6.8	8.1	7.4	6.6	7.2	7.4	7.4	8.2	6.4
Lung and bronchus	6.5	6.7	9.0	7.6	7.1	3.6	10.2	4.8	4.3	7.9
Prostate	18.4	17.8	12.9	12.3	18.3	22.6	11.4	13.1	12.6	13.2
Others	18.7	19.9	20.7	19.2	17.4	17.6	19.4	19.2	20.4	17.7

Hematological	8.8	8.5	8.7	12.2	9.3	7.9	9.2	10.3	8.8	12.2
Urinary system	6.5	6.0	5.5	6.7	6.9	6.8	5.9	7.4	5.9	6.9
Cancer stage										
I	17.0	16.1	18.9	13.4	18.2	16.9	20.1	16.7	20.4	17.6
II	21.6	21.1	19.6	17.4	22.2	22.4	18.6	15.5	19.5	18.9
III	10.8	11.6	12.3	11.5	10.6	8.5	10.7	7.9	8.4	9.7
IV	6.7	7.8	6.7	8.5	6.4	3.4	6.2	3.7	3.7	5.7
Unknown	44.0	43.4	42.4	49.2	42.7	48.9	44.3	56.2	48.0	48.1
Number of other comorbidities										
No other condition	12.9	18.2	2.7	4.4	7.6	11.0	1.0	2.2	1.0	1.0
1 other condition	23.0	26.9	22.9	21.7	18.6	23.1	10.8	14.5	15.0	10.8
2 other conditions	22.2	22.1	24.0	22.0	22.2	23.4	16.8	19.3	24.0	16.4
3 other conditions	16.6	14.3	17.8	17.6	19.0	17.4	20.7	19.3	21.2	18.8
4 or more other conditions	25.3	18.5	32.6	34.3	32.5	25.1	50.8	44.7	38.9	53.0

*Percentage is column percentage for each of the parameters

Hospitalizations and ED Visits According to the Characteristics of the Study Population

There was on average 0.57 hospitalization per person-year in cancer patients with a maximum value of 31.6 admissions per person-year, and 0.74 ED visits per person-year, and the highest value was 87.6 visits per person-year during the study period. Increasing age, male sex, rural residence, lower-income quintile, late-stage cancer, and lung and digestive system cancer were associated with a higher number of hospitalizations and ED visits. Patients with mood disorders had more hospitalizations and ED visits compared to those without mood disorders. In contrast, cancer

patients with arthritis had a higher number of ED visits but a lower number of hospitalizations per person-year than patients without arthritis (Table 2).

Table 2.

Hospitalizations and ED visits According to the Characteristics of the Study Population

Characteristics	**Hospitalization PPY (Mean ± SD)**	**p-value**	**ED Visits PPY (Mean ± SD)**	**p-value**
Presence of mood disorders and arthritis		<0.0001		<0.0001
No arthritis/mood disorders	0.57 ± 0.92		0.66 ± 1.25	
Mood disorders only before cancer	0.73± 1.06		1.03 ± 1.68	
Mood disorders only after cancer	1.09 ± 1.33		1.20 ± 2.10	
Arthritis only before cancer	0.61 ± 0.89		0.84 ± 1.37	
Arthritis only after cancer	0.40± 0.62		0.61 ± 0.96	
Bothe the conditions before cancer	0.86 ±1.12		1.39 ± 2.60	
Both the conditions after Cancer	0.81 ± 1.10		1.20 ± 2.20	
Mood disorders before and arthritis after cancer	0.58 ± 0.85		1.14 ± 1.64	
Arthritis before and mood disorders after cancer	1.10 ± 1.30		1.37 ± 2.11	
Age Group		<0.0001		<0.0001
18-44	0.40 ± 0.91		0.62 ± 1.22	
45-64	0.48 ± 0.87		0.66 ± 1.32	
>65	0.69 ± 0.89		0.83 ± 1.32	
Sex		<0.0001		<0.0001
Male	0.62 ± 0.93		0.77 ± 1.39	
Female	0.53 ± 0.85		0.71 ± 1.24	
Income Quintile		<0.0001		<0.0001

Q1	0.65 ± 0.95		0.98 ± 1.72	
Q2	0.60 ± 0.91		0.81 ± 1.35	
Q3	0.58 ± 0.91		0.68 ± 1.13	
Q4	0.55 ± 0.87		0.61 ± 1.02	
Q5	0.51 ± 0.83		0.56 ± 0.95	
Ethnic Concentration		<0.0001		<0.0001
Q1	0.64 ± 0.95		1.14 ± 1.81	
Q2	0.60 ± 0.91		0.98 ± 1.42	
Q3	0.56 ± 0.86		0.85 ± 1.21	
Q4	0.54 ± 0.86		0.78 ± 1.09	
Q5	0.52 ± 0.85		0.74 ± 1.03	
Place of Residence		<0.0001		<0.0001
Rural	0.68 ± 1.03		1.26 ± 2.23	
Urban	0.56 ± 0.87		0.66 ± 1.07	
Type of Cancer		<0.0001		<0.0001
Breast	0.34 ± 0.55		0.59 ± 0.98	
Colon and rectum	0.71 ± 0.90		0.78 ± 1.33	
Digestive system except for colon and rectum	1.08 ± 1.23		1.11 ± 1.95	
Female genital	0.58 ± 0.91		0.72 ± 1.30	
Lung and bronchus	1.03 ± 1.09		1.17 ± 1.74	
Prostate	0.34 ± 0.53		0.57 ± 0.97	
Others	0.50 ± 0.89		0.69 ± 1.34	
Haematological	0.74 ± 1.18		0.85 ± 1.46	
Urinary system	0.73 ± 0.98		0.87 ± 1.35	
Cancer Stage		<0.0001		<0.0001
I	0.37 ± 0.62		0.59 ± 1.06	
II	0.43 ± 0.67		0.63 ± 1.07	
III	0.79 ± 1.00		0.91 ± 1.47	
IV	1.17 ± 1.24		1.24 ± 1.90	
Unknown	0.58 ± 0.93		0.74 ± 1.34	
Number of Other Comorbidities		<0.0001		<0.0001
0	0.37 ± 0.83		0.48 ± 1.06	
1	0.43 ± 0.81		0.57 ± 1.07	
2	0.44 ± 0.83		0.67 ± 1.23	
3	0.58 ± 0.85		0.78 ± 1.27	
4+	0.87 ± 0.99		1.06 ± 1.63	

Tables 2 shows that mood disorders were associated with significantly increased annual average hospitalizations and ED visits to cancer patients. Mood disorders diagnosed after cancer was

associated with higher average annual hospitalizations and ED visits compared to mood disorders diagnosed before cancer. Then again, arthritis when diagnosed before cancer was linked to substantially increased ED visits without much impact on hospitalizations. In contrast to mood disorders, arthritis when diagnosed after cancer was associated with both lower hospitalizations and ED visits. However, average annual hospitalizations and ED visits were quite high in cancer patients having both arthritis and mood disorders irrespective of the time of diagnosis of these conditions. HCU also increased with the co-occurrence of other chronic conditions. Among the other covariates, increased age, male sex, rural resident, digestive system cancer except for colorectal, lung cancer, and stage III and IV cancer were associated with higher utilization of health care services.

Adjusted Impact of Arthritis and Mood Disorders on Hospitalizations of Cancer Patients

A negative binomial model was fitted to examine the impact of arthritis and mood disorders on the mean annual hospitalization of cancer patients adjusted for age, sex, place of residence, income quintiles, ethnic concentration, stage and type of cancer, and the number of other comorbidities (Table 3).

Table 3.

Adjusted Impact of Arthritis and Mood Disorders on the Hospitalization of Cancer Patients Adjusted for Sociodemographic and Clinical Variables

Characteristics		IRR	95% CI of IRR
Presence of Arthritis and Mood Disorders (ref= no arthritis /mood disorders)	Mood disorders only before cancer	1.19	1.14-1.24
	Mood disorders only after cancer	1.65	1.59-1.71
	Arthritis only before cancer	0.99	0.98-1.00

Characteristics		IRR	95% CI of IRR
	Arthritis only after cancer	0.75	0.74-0.76
	Both arthritis and mood disorders before cancer	1.25	1.20-1.29
	Both arthritis and mood disorders after cancer	1.28	1.20-1.37
	Mood disorders before and arthritis after cancer	1.01	0.92-1.10
	Arthritis before and mood disorders after cancer	1.59	1.53-1.65
Age Group (ref = 18-44)	45-64	1.02	1.01-1.04
	>=-65	1.21	1.19-1.23
Sex (ref=female)	Male	1.18	1.17-1.19
Rural (ref = no)	Yes	1.14	1.12-1.15
Income Quintile (ref = Q1)	Q2	0.95	0.94-0.96
	Q3	0.94	0.93-0.95
	Q4	0.91	0.90-0.92
	Q5	0.87	0.85-0.88
Ethnic Concentration Quintile (ref = Q1)	Q2	0.99	0.98-1.00
	Q3	0.96	0.94-0.97
	Q4	0.93	0.91 -0.94
	Q5	0.89	0.87-0.90
Cancer Types (ref= others)	Breast	0.82	0.80-0.83
	Colon and rectum	1.18	1.16-1.20
	Digestive system except colon and rectum	1.83	1.80-1.86
	Female genital	1.36	1.33-1.39
	Hematological	1.29	1.27-1.31
	Lung and bronchus	1.55	1.53-1.58
	Prostate	0.57	0.56-0.58
	Urinary system	1.18	1.16-1.20

Characteristics		IRR	95% CI of IRR
Presence of other comorbid conditions (ref = no other conditions)	1 other condition	1.07	1.05-1.09
	2 other conditions	1.18	1.17-1.20
	3 other conditions	1.34	1.32-1.37
	4 or more other conditions	1.91	1.88-1.94
Cancer stage (ref = stage I)	II	1.42	1.40-1.44
	III	2.04	2.00-2.07
	IV	2.87	2.82-2.92
	Unknown	1.50	1.48-1.53

Table 3 showed that the average annual number of hospitalizations was 19% greater in patients with mood disorders only present before cancer, while it was 65% higher among patients who developed mood disorders only after cancer, compared to patients without mood disorders and arthritis. In contrast, arthritis was associated with lower hospitalization whether it was developed before or after cancer. Cancer patients with both mood disorders and arthritis before and after cancer had 25% and 28% higher hospitalization rates respectively compared to those without any mood disorders or arthritis. Again, when cancer patients with arthritis had mood disorders developing after cancer, their hospitalization rates increased by 59% compared to those without any of the conditions. Older age groups, male sex, rural residents, and certain types of cancers were associated with an increased number of hospitalizations.

The interaction with other comorbidities was significant (results not shown), and stratified analysis according to MMB level was performed to examine whether the impact of arthritis and mood disorders on mean annual hospitalizations varied by the level of MMB (Table 4). The results showed that mood disorders alone occurring before cancer increased hospitalizations significantly when the patients had one or more other comorbid conditions. Mood disorders after cancer were

related to higher hospitalizations per person-year at all MMB level. The impact was highest when the patients had no other comorbid conditions but similar across all other MMB levels. On the other hand, the null impact of arthritis occurring before or after cancer was also comparable across the multimorbidity level (i.e. 1 condition, 2, 3, 4, or more conditions). The co-occurrence of mood disorders and arthritis after cancer increased hospitalizations the most when the patients had no other chronic conditions (Table 4).

Table 4.

Impact of Arthritis and Mood Disorders on the Hospitalization of Cancer patients by Multimorbidity level (ref = no arthritis/mood disorders)

Arthritis/ Mood disorders	**No other conditions IRR (CI)**	**1 other condition IRR (CI)**	**2 other conditions IRR (CI)**	**3 other conditions IRR (CI)**	**4 other conditions IRR (CI)**
Mood disorders only					
Before cancer	1.19 (0.86-1.61)	1.17 (1.05-1.30)	1.24 (1.13-1.36)	1.07 (0.96-1.18)	1.21 (1.14-1.28)
After cancer	3.08 (2.59-3.66)	1.67 (1.52-1.84)	1.68 (1.55-1.83)	1.77 (1.62-1.92)	1.45 (1.37-1.53)
Arthritis only					
Before cancer	1.06 (1.02-1.10)	1.00 (0.98-1.02)	0.96 (0.94-0.98)	0.98 (0.96-1.00)	1.00 (0.98-1.01)
After cancer	0.75 (0.71-0.79)	0.72 (0.69-0.74)	0.71 (0.68-0.73)	0.73 (0.70-0.76)	0.80 (0.78-0.82)
Both arthritis and mood disorders					
Before cancer	1.43 (0.88-2.21)	1.38 (1.21-1.57)	1.07 (0.96-1.19)	1.20 (1.11-1.31)	1.28 (1.22-1.34)
After cancer	1.81 (1.09-2.86)	1.09 (0.86-1.36)	1.34 (1.13-1.59)	1.24 (1.06-1.44)	1.28 (1.18-1.39)
Mood disorders before and arthritis after cancer	3.83 (1.87-7.40)	0.83 (0.59-1.13)	0.79 (0.62-0.99)	0.93 (0.75-1.13)	1.09 (0.97-1.22)
Arthritis before and mood disorders after Cancer	2.04 (1.31-3.08)	1.88 (1.65-2.14)	1.60 (1.44-1.77)	1.70 (1.56-1.85)	1.49 (1.42-1.56)

*IRR adjusted for age, sex, residence, income, ethnic concentration, cancer type, stage, and the number of additional comorbidities.

Adjusted Impact of Arthritis and Mood Disorders on the ED Visits of Cancer Patients

To examine the adjusted impact of arthritis and mood disorders on the ED visits of cancer patients, we also performed a negative binomial model. Table 5 showed that both arthritis and mood disorders were separately and jointly associated with increased emergency visits among cancer patients, except that arthritis alone occurring after cancer significantly decreased ED visits. When patients already had arthritis at the time of cancer diagnosis, mood disorders developing after cancer was associated with a 74% increased rate of ED visits, and when both the conditions developed before cancer, the rate of ED visits increased by 75%.

Table 5.

Impact of Mood Disorders and Arthritis on the ED Visits of Cancer patients Adjusted for Sociodemographic and Clinical Variables

Characteristics		**IRR**	**95% CI of IRR**
Presence of Arthritis and Mood Disorders (ref = no arthritis/mood disorders)	Mood disorders only before cancer	1.41	1.36-1.47
	Mood disorders only after cancer	1.55	1.49-1.61
	Arthritis only before cancer	1.20	1.19-1.21
	Arthritis only after cancer	0.97	0.96-0.98
	Both arthritis and mood disorders before cancer	1.75	1.69-1.81
	Both arthritis and mood disorders after cancer	1.60	1.50-1.69
	Mood disorders before and arthritis after cancer	1.62	1.51-1.74
	Arthritis before and mood disorders after cancer	1.74	1.68-1.81
Age (ref = 18-44)	45-64	0.83	0.82-0.84
	>=65	0.85	0.84-0.87
Sex (ref =female)	Male	1.11	1.10-1.12

Rural (ref = no)	Yes	1.63	1.62-1.65
Income Quintile (ref =Q1)	Q2	0.90	0.89-0.91
	Q3	0.86	0.85-0.87
	Q4	0.82	0.81-0.83
	Q5	0.76	0.75-0.77
Ethnic Concentration	Q2	0.93	0.92-0.94
Quintile (ref = Q1)	Q3	0.86	0.85-0.87
	Q4	0.78	0.77-0.79
	Q5	0.68	0.67-0.69
Cancer Types (ref = others)	Breast	0.96	0.94-0.97
	Colon and rectum	1.01	0.99-1.02
	Digestive system except colon and rectum	1.50	1.47-1.52
	Female genital	1.17	1.15-1.19
	Hematological	1.13	1.12-1.15
	Lung and bronchus	1.37	1.35-1.39
	Prostate	0.76	0.74-0.77
	Urinary system	1.09	1.07-1.10
Presence of other comorbid	1 other condition	1.18	1.16-1.20
conditions (ref= no other	2 other conditions	1.37	1.35-1.39
conditions)	3 other conditions	1.56	1.54-1.59
	4 or more other conditions	2.06	2.03-2.10
Cancer stage (ref = stage I)	II	1.20	1.18-1.22
	III	1.53	1.51-1.55
	IV	2.05	2.01-2.08
	Unknown	1.23	1.21-1.24

We tested the interaction between arthritis, mood disorders, and other comorbid conditions in the model. Though the interaction was significant, stratified analysis by multimorbidity level showed that the differences in risk ratios of ED visits were related to the main exposure rather than MMB levels. As such, there were differences in the impact of arthritis and mood disorders on ED visits, but this impact remained similar within the level of comorbidities. Mood disorders increased the risk of ED visits more compared to arthritis and the difference was larger when the patients had no or one other chronic condition. The presence of both mood disorders and arthritis before and after cancer was associated with an increased risk of ED visits at all multimorbidity levels (Table 6).

Table 6.

Impact of Arthritis and Mood Disorders on ED Visits Stratified by the Number of Other Comorbidities (ref = no arthritis/mood disorders)

Arthritis/ Mood disorders	No other conditions IRR (CI)	1 other condition IRR (CI)	2 other conditions IRR (CI)	3 other conditions IRR (CI)	4 other conditions IRR (CI)
Mood disorders only					
Before cancer	1.24 (0.93-1.63)	1.53 (1.40-1.67)	1.44 (1.33-1.56)	1.26 (1.14-1.38)	1.40 (1.31-1.49)
After cancer	2.00 (1.65-2.42)	1.67 (1.52-1.82)	1.49 (1.37-1.63)	1.51 (1.38-1.66)	1.47 (1.38-1.56)
Arthritis only					
Before cancer	1.19 (1.16-1.23)	1.20 (1.19-1.22)	1.18 (1.16-1.21)	1.18 (1.16-1.21)	1.21 (1.18-1.22)
After cancer	0.95 (0.91-1.00)	0.95 (0.93-0.98)	0.96 (0.93-0.98)	0.97 (0.94-1.00)	0.99 (0.97-1.02)
Both arthritis and mood disorders					
Before cancer	1.37 (0.87-2.07)	1.80 (1.61-2.01)	1.65 (1.51-1.80)	1.69 (1.56-1.82)	1.76 (1.69-1.84)
After cancer	1.76 (1.10-2.72)	1.49 (1.24-1.78)	1.69 (1.46-1.95)	1.43 (1.24-1.65)	1.58 (1.46-1.84)
Mood disorders before and arthritis after cancer	0.99 (0.32-2.46)	2.07 (1.70-2.49)	1.65 (1.41-1.92)	1.49 (1.27-1.74)	1.50 (1.35-1.67)
Arthritis before and mood disorders after Cancer	1.69 (1.10-2.52)	2.06 (1.83-2.31)	1.84 (1.67-2.02)	1.92 (1.76-2.08)	1.60 (1.52-1.68)

Discussion

The study evaluated the impact of mood disorders and arthritis on the health care utilization by cancer patients as measured by hospitalizations and ED visits per person-year. The study findings showed that mood disorders were associated with increased hospitalizations and ED visits among cancer patients irrespective of developing before or after cancer. This finding was in alignment with the previous research (Mausbach & Irwin, 2017; Niazi et al., 2018). Niazi et al. (2018) found

that multiple myeloma patients with depression had a 41% higher risk of inpatient admission and 37% increased risk of ED visits (Niazi et al., 2018). In contrast, we found a 65% higher risk of hospitalizations and a 55% higher risk of ED visits in cancer patients diagnosed with mood disorders after cancer. Besides, mood disorders diagnosed before cancer was also associated with 19% more hospitalizations and 41% more ED visits. Niazi et al. (2018) conducted their study within the Medicare beneficiaries of the United States, who were older and, they included patients with a specific type of blood cancer, i.e. multiple myeloma whereas, we included all the patients with cancer diagnosed within a specified period. They identified the patients with a specific mood disorder i.e. depression and they did not account for the time of development of the condition (before/after cancer). Moreover, they only considered whether the patients had hospitalizations and ED visits without considering the number of visits. This might explain the discrepancy in the risk of ED visits between their study and our study. Mausbach & Irwin (2017) found that depression in cancer patients was associated with a 76% higher rate of health services visits (Mausbach & Irwin, 2017). Here the authors included all the visits to the different health services providers including hospital admissions and ED visits. Depressed cancer patients had 2.45 times higher odds of ED visit and 1.81 times higher odds of at least one hospitalization in one year compared to the non-depressed patients (Mausbach & Irwin, 2017). However, in calculating the risk of hospitalization and ED visits, encounters with the health services in the first year of cancer diagnosis were taken into account without considering the actual number of hospitalizations or ED visits. As HCU is generally higher in the first year of cancer diagnosis, Mausbach & Irwin (2017) found a higher odds ratio of HCU associated with depression.

On the other hand, arthritis alone when diagnosed before cancer was associated with 20% increased ED visits among cancer patients while having no impact on hospitalizations. However,

when arthritis was diagnosed after cancer it was related to lower hospitalizations and ED visits. Wright et al. (2010) found that patients with knee osteoarthritis had more annual emergency visits, hospitalizations, and physician visits compared to those without osteoarthritis, and the HCU increased with the presence of comorbidities including cancer (Wright et al., 2010). This was in contrast with our findings, with regards to both hospitalizations and ED visits. The study by Wright et al. (2010) included the general population without cancer and described that most of the hospitalizations in arthritis patients were due to joint replacement (Wright et al., 2010). As cancer patients were mostly in severe condition and joint replacement is unlikely among them, arthritis-related hospitalizations should be lower in cancer patients with arthritis. Moreover, the development of arthritis and the associated pain might lead to an increased encounter with the primary care physicians which has been shown to decrease hospitalizations and ED visits (Mileski et al., 2020; Rosano et al., 2013; Shi, 2012). Arthritis in combination with mood disorders before or after cancer was associated with higher hospitalizations per person-year in comparison to the cancer patients without arthritis and mood disorders. Interestingly, when cancer patients diagnosed with mood disorders before their cancer developed arthritis, there was no increase in hospitalizations. On the contrary, the development of mood disorders after cancer in patients with cancer and arthritis led to a 59% increase in hospitalizations. So, mood disorders alone or in combination with arthritis were related to higher hospitalization in cancer patients. It can be assumed that the development of a new psychological condition in cancer patients might increase health care utilization as evidenced by literature (McDermott et al., 2018).

We performed a stratified analysis by the level of MMB and found that the impact of mood disorders diagnosed before cancer on hospitalizations was highest in patients having one or more co-occurring conditions. These findings were in alignment with previous evidence that the

comorbidity index was a significant predictor of HCU including hospitalizations and ED visits in cancer patients with depression (Mausbach & Irwin, 2017). The association between mood disorders after cancer and hospitalizations was most pronounced in patients with no other comorbidities and similar across all other MMB level. On the other hand, arthritis alone when diagnosed after cancer was associated with lower hospitalizations and ED visits across all MMB level. In complex cancer patients, the pain associated with arthritis might be misattributed as the pain of cancer and as such, health services use might be largely due to cancer and other comorbidities. While considering the joint effect of arthritis and mood disorders on HCU, our study showed that the impact of mood disorders and arthritis developing before cancer on HCU did not vary statistically among the different MMB levels. Arthritis and mood disorders together developing after cancer were associated with highest increase in HCU among the patients with no other comorbidities. In cancer patients with MMB, any increase in hospitalizations and ED visits might be mostly attributed to cancer or other severe chronic conditions rather than arthritis and mood disorders. One finding from the study showed that when arthritis developed after cancer in patients with mood disorders before cancer, and without any other comorbidities, there was three folds increase in hospitalizations. Perhaps, the newly diagnosed arthritis and the associated pain was associated with increased hospitalization as these patients were devoid of any other comorbidities and any new symptoms were attributed to their hospitalizations. We also found that hospitalizations and ED visits were higher among elderly patients, males, rural residents, and in patients with late-stage cancer. These findings are consistent with the results of the previous study (Lash et al., 2017).

Strengths and Limitations

The study is mainly limited because of the operationalization of exposure. We considered the presence of mood disorders and arthritis as exposure without accounting for the time of occurrence when developing after a cancer diagnosis. So, some patients might develop these conditions after the outcome, i.e. hospitalizations and ED visits, and thus this would not be responsible for their HCU. However, the distinction between diagnosis before and after cancer is key. As most of the patients developed their mood disorders and arthritis before their cancer and HCU were counted after the cancer diagnosis, a temporal relationship could be established between arthritis, mood disorders, and HCU. Moreover, the mean time of development of mood disorders and arthritis after cancer was much lower than the mean follow-up period. So, it was expected that the diagnosis of mood disorders and arthritis would contribute towards the HCU of most patients. Still, there would be some misclassification of the exposure definition which would certainly over-estimate the impact of mood disorders and arthritis on the HCU of cancer patients.

The study was a secondary analysis of data from health administrative databases and included only those patients having contact with the health care system contributing to potential selection bias. However, the sample was large enough to get a robust estimate of long term HCU by cancer patients. Other limitations are related to the predictor's measurement. The cases of arthritis, mood disorders, and other chronic conditions were identified using administrative databases, which may contribute to the misclassification of these conditions in cancer patients. In administrative databases, there are possible errors in coding conditions as well as these databases show little difference in coding complicacy of a condition with comorbidities (Mazzali et al., 2016). This might result into misclassification leading to higher count and impact of comorbities on the study outcomes. In OHIP, there are three codes for mood disorders, namely 296 (episodic mood

disorders), 300 (cyclothymic disorder), and 311 (Depressive Disorder NOS). We included only 296 from OHIP and ICD-10 codes from DAD and NACRS for identifying mood disorders. Moreover, under-reporting of psychiatric conditions and other comorbidities in cancer patients may also lead to misclassification bias although linking several databases enabled us to appropriately measure the prevalence of the chronic conditions. Moreover, Canadian administrative databases have 85% accuracy for diagnostic codes (Juurlink et al., 2006). So, using administrative databases could under estimate the prevalence of chronic conditions causing dilution of their impact on health care utilizations.

In this study, only 16 chronic conditions excluding arthritis and mood disorders were used to define MMB which creates a chance for misclassifying the cancer patients according to MMB level. There are other severe chronic conditions like congenital anomalies, thyroid diseases, glaucoma which were not taken into account in the study due to the unavailability of data. However, literature suggested that including 11 or 12 conditions is optimum for obtaining the population prevalence of MMB, and adding more conditions only increases complexity (Diederichs et al., 2011; Fortin et al., 2012; van den Akker et al., 1998). We also only counted the number of conditions and did not account for severity, whereas one severe condition might impact HCU more than having two or three less severe conditions.

Despite the limitations, the study had many strengths too. It was a population-based retrospective cohort study. Although there was some misclassification in defining the exposure, we were able to establish a temporal relationship between arthritis, mood disorders, and health services use in cancer patients specifically among the patients who were diagnosed with those conditions before cancer. The study was conducted with health administrative data including all the adult patients with cancer in Ontario, and we got an estimate of hospitalization and ED visits

in cancer patients at the population level. Canadian health administrative databases have extremely high data coverage and accuracy (Juurlink et al., 2006). Mood disorders, arthritis, and other comorbidities included in the study were defined using algorithms based on administrative databases widely cited in the literature to address MMB where applicable or two physicians' visit in a two years period or one hospital admission (Austin et al., 2002; Fiest et al., 2014; A. S. Gershon et al., 2009; Andrea S Gershon et al., 2009; Hux et al., 2002; Jaakkimainen et al., 2016; Schultz et al., 2013; Widdifield et al., 2014).

We performed a stratified analysis by the number of comorbidities to observe whether the association between arthritis, mood disorders, and HCU was modified by the number of other co-occurring conditions. We found that the association between arthritis, mood disorders, and HCU varied by the time of occurrence of mood disorders and arthritis (before/after cancer) as well as by the multimorbidity level. However, mood disorders diagnosed before or after cancer was associated with a higher increase of HCU than arthritis. Besides, in complex cancer patients, the number of co-occurring conditions was an important predictor of higher use of health services. This explained the importance of addressing MMB, specifically mood disorders in cancer patients to decrease their use of health services. The patients were diagnosed with cancer at a different time and entered the cohort as soon as they were diagnosed with cancer. As a result, the follow-up time was different for each patient and between 5-15 years or more. So we calculated the average annual health care utilization accounting for hospitalization and ED visits per person-year. The long follow-up period provided a large window to assess whether mood disorders and arthritis have an impact on health care utilization. It has been shown that the duration and chronicity of depressive symptoms is an important predictor of increased health services use (Roberts et al., 2018). In our

study, we followed the patients for a longer period which might enable us to better understand the impact of mood disorders and arthritis on the health care utilization of cancer patients.

Implications of the Findings

The study revealed that mood disorders were associated with both increased hospitalizations and ED visits significantly in cancer patients while arthritis was linked to only increased ED visits but decreased hospitalizations. The retrospective cohort study could establish a temporal relationship between arthritis, mood disorders, and HCU and as we looked at the average annual hospitalizations and ED visits for a substantial period of time at the population level, it enabled us to generate and test our hypotheses on the potential role of MMB including arthritis and mood disorders on the HCU of cancer patients. We hypothesized and our study provided evidence that multimorbidity including arthritis and mood disorders is associated with greater use of health services in cancer patients. The study also revealed that the impact of arthritis and mood disorders did not vary significantly across all the levels of multimorbidity; however, mood disorders occurring after cancer increased HCU most when the patients had one or more other comorbidities. On the other hand, arthritis alone or in combination with mood disorders was associated with with higher HCU when the patients had no other chronic conditions. Then again, both hospitalizations and ED visits in cancer patients increased with the number of co-occurring conditions. These findings show the importance of addressing MMB, especially mood disorders to decrease HCU that may be avoidable in cancer patients. The findings from the study add to the literature and helped to understand the predisposing factors for higher HCU in cancer patients. Future prospective cohort studies on the impact of MMB on the HCU and identifying the specific chronic conditions or disease clusters causing higher HCU will enable us to focus on the complex cancer patients having the highest health care needs. Long-standing conditions in patients with cancer

need to be addressed early and proper management of the chronic conditions will decrease their health service use and eventually improve patients' quality of life while reducing the burden on the health care system.

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Appendices

Appendix A: Administrative Databases Used in the Study and the Corresponding Variables

Database	Description	Variables
Registered Persons Database (RPDB)	Includes data on all person eligible for the Ontario Provincial Health care program and provides demographic information like age, sex, date of birth, death, residence, and neighborhood income	Age, sex, residence, income quintile
Discharge Abstract Database (DAD)	Hospital inpatient data. It includes data on hospital admission, discharge, length of stay, primary diagnosis, other diagnoses, procedures, and interventions	Arthritis, mood disorders, and other comorbidities using the ICD codes, date/year of diagnosis, hospitalization
Ontario Health Insurance Plan (OHIP) claims	Physician's claim database. Includes the date of visit, diagnosis, procedures such as laboratory tests and vaccination	Arthritis, mood disorders, and other comorbidities using the ICD codes, date/year of diagnosis
National Ambulatory Care Reporting	Includes hospital outpatient data, diagnosis, day surgeries, and Emergency department visits	Arthritis, mood disorders, and other comorbidities using the

System (NACRS)		ICD codes, date/year of diagnosis, ED visits
Ontario Cancer Registry (OCR)	Provincial database of all the residents of Ontario having a diagnosis of cancer. Contains demographic and clinical information including the date of diagnosis, primary cancer site, cancer stage, and death	Age, sex, date of birth, death, cancer type, date of cancer diagnosis
Ontario Marginalization Index (ON-Marg)	The Ontario Marginalization Index is a measure of inequalities between the geographical areas based on four dimensions; residential instability, material deprivation, ethnic concentration, and dependency	Ethnic concentration quintiles

Appendix B: ICD Codes for Chronic Conditions

Condition	ICD 9 / OHIP	ICD 10
AMI	410	I21, I22
Arthritis – Osteoarthritis	715	M15-M19
Arthritis - Other Arthritis (Synovitis, Fibrositis, Connective tissue disorders, Ankylosing spondylitis, Gout Traumatic arthritis, pyogenic arthritis, Joint derangement, Dupuytren's contracture, Other MSK disorders)	727, 729, 710, 720, 274, 716, 711, 718, 728, 739	M00-M03, M07, M10, M11-M14, M20-M25, M30-M36, M65-M79
Arthritis - Rheumatoid arthritis		M05-M06
Asthma	493	J45
Cancer	140-239	C00-C26, C30-C44, C45-C97
Cardiac Arrythmia	427.3 (DAD) / 427 (OHIP)	I48.0, I48.1
CHF	428	I500, I501, I509
COPD	491, 492, 496	J41, J43, J44
Dementia	290, 331, 797 (OHIP) / 290.0, 290.1, 290.3, 290.4, 290.8,	F000, F001, F002, F009, F010, F011, F012, F013,

	290.9, 294.1, 294.8, 294.9, 331.0, 331.1, 331.2, 797 (DAD)	F018, F019, F020, F021, F022, F023, F024, F028, F03, F051, F065, F066, F068, F069, F09, G300, G301, G308, G309, G310, G311, R54
Mood Disorders	296	F30-F34, F38, F39
Diabetes	250	E08 - E13
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15
Osteoporosis	733	M81 M82
Renal failure	403, 404, 584, 585, 586, v451	N17, N18, N19, T82.4, Z49.2, Z99.2
Stroke	430, 431, 432, 434, 436	I60-I64
Coronary syndrome (excluding MI)	411-414	I20, I22-I25
Other mental disorders (substance use disorder, psychotic disorder, anxiety, stress reaction-specifically PTSD, personality disorder)	291, 292, 303, 304, 305, 295, 298, 297, 300, 308, 301	F10-F19, F55, F20-F29, F40-F42, F93, F43, F60

Appendix C

Univariate Analysis of Time to Mood Disorders, Arthritis, Follow-up Time and Time to Death in Patients with Mood disorders and Arthritis Developing after Cancer (in days)

Variable	Mean	Standard Deviation	25th percentile	Median (50th percentile)	75th percentile	Mode
Time to diagnosis of mood disorders	1178.66	1009.12	357	881	1786	42
Time to the end of the study (follow up time for the living patients) in patients with mood disorders	3791.38	1013.60	2945	3834	4677	2760
Time to death (follow up time for the patients who died during the study period) in patients with mood disorders	1919.83	1186.59	896	1677	2739	874
Time to diagnosis of arthritis	1252.37	967.52	466	1010	1842	385
Time to the end of the study (follow up time for the living patients) in patients with arthritis	3951.57	993.60	3172	4069	4809	5112
Time to death (follow up time for the patients who died during the study period) in patients with arthritis	2441.25	1233.07	1424	2351	3375	958

Chapter 6: Discussion

The purpose of this thesis is to study whether there is an association between arthritis and the development of mood disorders in cancer patients considering the level of multimorbidity and to examine the impact of arthritis and mood disorders on their health care utilization. The findings showed that arthritis was not associated with the risk development of mood disorders in cancer patients; rather, the number of other comorbidities had a significant impact. However, the null association between arthritis and mood disorders did not alter in the presence of other co-occurring conditions. Another key finding was that cancer patients with both arthritis and mood disorders experienced higher HCU and mood disorders were associated with the highest increase in HCU.

6.1 Main Findings

6.1.1 The Incidence of Mood Disorders in Cancer Patients was 16.9 per 1000 and did not Vary According to the Presence of Arthritis

The crude cumulative incidence of mood disorders in the study population was 16.9 (95% CI 16.6-17.3) per 1000. The incidence was similar among patients with or without arthritis (17.0/1,000 vs. 16.8/1,000). Most of the studies looked at the prevalence of mood disorders but there is limited evidence in the literature on the incidence of mood disorders in cancer patients (Hung et al., 2013; Zhu et al., 2017). Hung et al. (2013) followed up a cohort of breast cancer patients in Taiwan and found that the incidence of mood disorders in these patients was 196/1,000 population which was higher than our study's estimate. They defined mood disorders with ICD-9 codes and included anxiety with mood disorders causing a much higher estimate than our study (Hung et al., 2013). On the other hand, Zhu et al. (2017) calculated the incidence of mood disorders among cancer patients in Sweden as 13.99 per 1,000 population which was slightly lower than our result as they considered only major depressive disorder.

Our study showed that arthritis was not associated with an increased risk of mood disorders in cancer patients. This contrasted with our hypothesis where it was assumed that arthritis would increase the risk of mood disorders in cancer patients. In previous research, there were no explicit tests of increased risk of mood disorders associated with arthritis among cancer patients specifically. However, cancer and arthritis were individually implicated as risk factors for mood disorders in the literature (He et al., 2008; Hung et al., 2013; Jeong et al., 2017). Among breast cancer patients, the incidence of mood disorders was 33% higher than those without cancer (Hung et al., 2013). Specifically, breast cancer patients had a two times higher risk of developing major depressive disorders and bipolar disorders (Hung et al., 2013). This was a unique finding in this study as most other studies found an increased risk of depression in cancer patients while this study also reported a higher incidence of bipolar disorder. The authors discussed that hormones used in breast cancer treatment as well as genetic mutation could increase the risk of bipolar disorders among these patients (Hung et al., 2013). On the other hand, van 't Land et al. (2010) found a 1.9 times higher risk of developing mood disorders in patients with arthritis (van 't Land et al., 2010). Hsu et al. (2014) reported two folds higher incident rates of bipolar disorder in patients with rheumatoid arthritis. The authors described that the inflammatory process of joints involved in rheumatoid arthritis might be associated with the inflammation of the brain, eventually increasing the risk of developing bipolar disorders (Hsu et al., 2014; Lampa et al., 2012). We found a null association between arthritis and the development of mood disorders in cancer patients. One possible explanation for our results may be that the pain associated with arthritis and the severity of cancer might cause a misattribution of the symptoms of depression and other mental conditions. Moreover, there might be overlapping of symptoms, i.e. pain is common in both cancer and arthritis; as such, depression associated with pain could be attributed mostly to cancer rather than

arthritis. Another possibility is inadequate care about the mental health of cancer patients and ignoring their psychiatric symptoms. When stratified by cancer types, patients with lung, prostate, and urinary system cancers showed a higher risk of mood disorders associated with arthritis at the baseline while breast cancer patients with arthritis showed a lower baseline risk. The impact of arthritis on the development of mood disorders decreased with time in the lung, prostate, and urinary system cancer, while the impact of arthritis increased in breast cancer patients with time. In cancers with poor prognosis, i.e. lung cancer, depression is mostly associated with the adverse outcomes of the cancer. Chronic conditions like arthritis could become less important with the advancement of cancer and might not increase the risk of mood disorders including depression among these patients. In contrast, breast cancer patients generally had longer survival, and likely to suffer from arthritis for a longer time. Suffering from arthritis for substantial time leads to disability, dependence on others, and eventually depression (Nicassio, 2010). This can possibly explain the higher impact of arthritis on the development of mood disorders over time. Nevertheless, Hung et al. (2013) found no association between autoimmune diseases, namely arthritis and mood disorders over time in their population-based cohort study on breast cancer patients in Taiwan (Hung et al., 2013).

6.1.2 The Number of Chronic Other Chronic Conditions (Multimorbidity) Constitutes an Important Factor for Mood Disorders Occurrence but does not Modify the Adjusted Impact of Arthritis

The risk of mood disorders in cancer patients increased with the multimorbidity level. This was consistent with the previous literature where the risk of depression was shown to be increased with the number of chronic conditions (Hartung et al., 2017; Massie, 2004). In a population-based study conducted in the United States, the authors reported increased odds of developing depression in

breast cancer patients with comorbidities and the risk was highest among those with four or more chronic conditions (Zoorob et al., 2019). However, stratified analyses by the number of co-occurring conditions showed that arthritis had no impact on the development of mood disorders, and this did not change whether the patients with cancer had no other conditions or one or more chronic conditions.

Among the other covariates increased age, stage IV cancer, certain cancer types, and death during the study period were significant risk factors for mood disorders. Similar results had been found in the literature (Nikbakhsh et al., 2014; Walker et al., 2014; Zoorob et al., 2019). Interestingly, in our study, male sex was linked to higher risk of mood disorders in contrast to literature where females are more likely to develop mood disorders (Caruso et al., 2017). However, the proportion of patients with two or more conditions was higher among males than females. Research showed that MMB is a known risk factor for the development of depression (Zoorob et al., 2019) and this could explain the higher risk of developing mood disorders among the males after adjusting for confounders. In our study, the crude incidence of mood disorders was higher among the age group 18-44 but when adjusted for other covariates, older age groups became a significant factor for developing depression. There are controversial findings in the literature regarding the impact of age on the risk of mood disorders. Nikbakhsh et al. (2014) reported that depression was more common among elderly people whereas Walker et al. (2014) described younger age as a risk factor for developing depression (Nikbakhsh et al., 2014; Jane Walker et al., 2014). Our study results followed the findings of Nikbakhsh et al. (2014) who were also focusing on cancer patients specifically.

6.1.3 Mood Disorders and Arthritis was Associated with Increased the Hospitalizations and ED Visits in Cancer Patients and Mood Disorders had Higher Impact on HCU than Arthritis

Both arthritis and mood disorders were associated with increased HCU in cancer patients. Cancer patients with arthritis diagnosed before cancer exhibited 20% (95% CI = 19-21%) more ED visits but slightly less hospital admission. Again, post-cancer diagnosis of arthritis was associated with lower hospitalizations and ED visits per person-year. On the other hand, pre-cancer diagnosis of mood disorders was linked to 19% (95% CI = 14-24%) more hospitalizations and 41% (95% CI = 36-47%) more ED visits. Then again, mood disorders diagnosed after cancer were related to higher increase in both hospital admissions (65%; 95% CI = 59-71%) and ED visits (55%; 95% CI = 49-61%). When arthritis and mood disorders were present together before cancer, there was an 25% (95% CI = 20-29%) increase in hospitalizations and 60% (95% CI = 50-69%) increase in ED visits respectively. Furthermore, the co-occurrence of arthritis and mood disorders after cancer led to 28% (95% CI = 20-37%) greater hospitalizations and 60% (95% CI = 50-69%) more ED visits. The study findings are in alignment with the previous literature to some extent (Himelhoch et al., 2004b; Mausbach & Irwin, 2017; McDermott et al., 2018). Mausbach & Irwin (2017) mentioned from their population-based study that depression increased the risk of ED visits by 3.05 times and at least one hospitalization in one year by 2.24 times (Mausbach & Irwin, 2017). Niazi et al. (2018) found that mood disorders were associated with 41% more hospitalizations, 37% higher ED visits, and 22% higher ambulatory service usage. A previous study found that pre-existing depression in cancer patients decreased HCU in comparison to patients without depression whereas, depression diagnosed after cancer had no statistically significant impact on HCU (McDermott et al., 2018). We found that mood disorders was associated with increased HCU in cancer patients irrespective of its time of development (before/after cancer). McDermott et al. (2018) considered only older

lung cancer patients with increased disease severity and lower survival. As such, they could not find a significant association between depression and HCU. Our study was a population-based study with a large sample including all the cancer patients surviving at least a year and yielded a significant impact of mood disorders diagnosed before and after cancer on the HCU of the patients.

Interestingly hospitalization was lower in patients with arthritis only and a possible hypothesis is that cancer patients with arthritis had frequent encounters with the health care system, particularly primary care. Research showed that primary care physicians and nurse practitioners could have a potential impact on decreasing hospital admission and ED visits in patients with various chronic conditions (Mileski et al., 2020; Rosano et al., 2013; Shi, 2012). In cancer patients with arthritis, the early diagnosis of complications and initiation of treatments at the primary care level could prevent further hospitalizations and ED visits. However, arthritis diagnosed before cancer was linked to higher ED visits. The disease process of arthritis follows a chronic inflammatory course, having arthritis for a longer time could lead to uncontrolled symptoms and eventually increase ED visits significantly.

6.1.4 The Impact of Arthritis and Mood Disorders on the HCU of Cancer Patients Varied by the Level of Multimorbidity. Mood disorders was associated with highest Increase in Hospitalizations in Patients Without any Co-occurring Conditions while Most Pronounced Impact for ED visits was Found among the Patients with One or More Chronic Conditions.

Stratified analyses by the level of multimorbidity showed that the impact of mood disorders before cancer on hospitalization was similar among the patients having none or one or more comorbidities. When mood disorders alone were diagnosed after cancer hospitalizations were highest when the patients had no other comorbidities but remained similar for one or more co-

morbidities. In complex cancer patients with multiple chronic conditions, hospital admissions might be related to other conditions rather than mood disorders. There might be misclassification bias as psychological conditions are generally under-reported in cancer patients resulting in dilution of the estimate of the impact of mood disorders at higher MMB levels. However, diagnosis of mood disorders was linked to increased ED visits similarly at all MMB level.

On the other hand, the impact of arthritis on the hospitalizations and ED visits of cancer patients was similar across levels of MMB. When mood disorders and arthritis both occurred either before or after cancer, there was a significant increase in hospitalizations and ED visits at all MMB levels. This explained that the impact of arthritis and mood disorders were mainly related to the main exposure and time of occurrence (before and after cancer) rather than the number of other comorbid conditions. However, MMB level (excluding arthritis and mood disorders) was a significant risk factor for hospitalization and ED visits. This finding was consistent with the results of the previous studies (Himelhoch, et al., 2004; Pitman et al., 2018; Roy et al., 2018). Literature suggested that the number of comorbidities was associated with HCU in cancer patients and an increasing number of comorbidities including arthritis and mood disorders increased ED visits in cancer patients (Johansson et al., 2004). Wright et al. (2010) found that cancer patients with different chronic conditions need more health care services compared to those without any comorbidities and the need for HCU increased with the number of chronic conditions which was similar to our study findings (Wright et al., 2010).

6.2 Limitation of the Study

The use of administrative data to diagnose the cases of arthritis and mood disorders was the main limitation of the study. Diagnosis of chronic conditions based on administrative data might cause misclassification bias. The participants in the study were cancer patients diagnosed between

2003-2013, surviving more than a year, and having contacts with the health care system. As we only included the patients having a valid health card, there was a chance of selection bias. The patients who survived less than a year were excluded to avoid reverse causality but that could lead to an underestimation of the incidence of mood disorders. We performed a sensitivity analysis to describe the association between arthritis and mood disorders in cancer patients surviving less than a year. The findings showed that arthritis and MMB were not linked to the risk of mood disorders in these patients. They had increased disease severity, and their depression was associated primarily with the worst prognosis of their cancer. As a result, arthritis, MMB, and other covariates did not have an impact on the risk of mood disorders in these cancer patients.

In cancer patients, due to the severity of the disease, other chronic conditions might be under-reported. So, there could be a possible underestimation of the incidence of mood disorders. Moreover, we are considering depression and bipolar disorder together as mood disorders while the pathological process and risk factors are different for those two types of mood disorders. Literature showed that cancer and arthritis are risk factors for depression while there is little evidence for their impact on the development of bipolar disorders (Hartung et al., 2017; Rathbun et al., 2018). We were not able to consider these two conditions separately in our database which might decrease the impact of arthritis on developing mood disorders. However, as the population prevalence of bipolar disorders is generally low (McDonald et al., 2015), it should not impact the study findings significantly. To determine MMB in cancer patients, only 16 chronic conditions were included in the study. The patients might have other comorbidities that were not included in the study leading to an underestimation of the burden of MMB. Moreover, the time of diagnosis of the chronic conditions was not taken into account which created misclassification of multimorbidity level diluting the impact of MMB on the development of mood disorders.

To assess the impact of arthritis and mood disorders on the HCU of cancer patients, we adopted a retrospective cohort study design. We considered that all the cases of mood disorders and arthritis were diagnosed before the outcomes (hospitalizations and ED visits per person-year). In fact, among the patients who were diagnosed with arthritis or mood disorders after their cancer might encounter the health care system before they developed those conditions. These patients were misinterpreted as exposed while they were actually not exposed. Thus, there was certainly some over-estimation of arthritis and mood disorders and associated HCU. However, as the average time for the development of mood disorders and arthritis was much lower than the average follow-up time, we expected that most patients developed mood disorders and arthritis well before to impact their HCU. The study did not consider the severity or type of chronic conditions while one severe condition could cause higher HCU than two or more less severe conditions. There were unmeasured confounders that were not considered in the study due to the unavailability of data.

6.3 Strengths of the Study

The first part of the thesis was a population-based retrospective cohort study that provided evidence for the temporal association between arthritis and mood disorders in cancer patients. We used the provincial administrative database, namely DAD, OHIP, NACRS for identifying chronic conditions including arthritis and mood disorders. An ICES investigative report on the Discharge Abstract Database described that the accuracy of demographic information was 97%, and diagnostic codes were 85% (Juurlink et al., 2006). In detecting the cases of rheumatoid arthritis, the Canadian administrative databases have 75-90% sensitivity, and 51-83% positive predictive value based on the algorithm used (Widdifield et al., 2014). The follow-up period for the cohort study was between 5-15 years and we could get long-term incidence rates of mood disorders and HCU in cancer patients. For classifying MMB level, 16 chronic conditions were considered

whereas previous evidence showed that including 11 or 12 conditions are optimum to get population prevalence of MMB (Diederichs et al., 2011; Fortin et al., 2012; van den Akker et al., 1998).

The retrospective cohort study assessing the association between arthritis, mood disorders, and HCU provided an estimate of the average annual HCU in cancer patients. The study also provides evidence for the temporal relationship between arthritis, mood disorders, and HCU in cancer patients and tested our hypothesis that MMB including mood disorders and arthritis increased HCU. We considered the time of diagnosis of mood disorders and arthritis and could demonstrate the differential impact of these conditions on the HCU of cancer patients when they developed alone or in combination before and after cancer. Stratified analyses were performed to see whether the association between arthritis, mood disorders, and HCU varied by the level of MMB and by different cancer types. Thus, we could identify the patients most probable of developing mood disorders as well as more likely to have higher HCU.

6.4 Epidemiological Implications: Internal and External Validity

In the first part of the study, we assessed the impact of arthritis on the development of mood disorders in cancer patients. In the second part, we examined the association between arthritis, mood disorders, and HCU of cancer patients. We identified patients with mood disorders using ICD-10 codes from DAD and NACRS and ICD-9 codes from OHIP. In OHIP there were three codes for mood disorders and among them, we considered the code specific for mood disorders. Besides, mood disorders were also identified using ICD-10 codes in hospitalizations data (DAD and NACRS). So, we most certainly achieved high specificity in the study while there was an underestimation of the incidence and prevalence of mood disorders in cancer patients. The prevalence of mood disorders estimated in the study was 3.52% which was much lower than the

annual prevalence of mood disorders (9%) in Canada in 2019 (Statistics Canada, n.d.). As only the codes specified for mood disorders were included in the study, the study might have less sensitivity while having high specificity. On the other hand, DAD has an accuracy of 85% for diagnostic codes which could decrease the sensitivity and specificity of the study as well (Juurlink et al., 2006).

The study population includes only those adult patients with cancer who had contacts with the health care system. Canada has a universal health care system, and OHIP provides health coverage to all the residents in Ontario, including the immigrants after their three months of the mandatory waiting period. As the study was population-based, so the selection bias was minimal and adjustment for main confounders contributed to good internal validity. The study analyzed data at the provincial level, and Ontario has the highest population in Canada. The findings of the study will apply to the Canadian population having similar access to the health care system as well as other high-income countries with comparable socio-demographic characteristics and healthcare access. Thus, the study has good external validity. The study included only those cancer patients who survived more than a year and the findings of the sensitivity analyses showed that arthritis was not associated with increased risk of developing mood disorders regardless of cancer patients' survival (more vs. less than a year). However, MMB was a significant risk factor for mood disorders in patients surviving more than a year and did not affect patients surviving less than a year. So, the findings may be more applicable for those patients surviving longer periods.

The second part of the thesis was a cohort study that could provide evidence of whether the increased HCU in a cancer patient with arthritis and mood disorders was originally related to these conditions. We felt that the retrospective cohort design was appropriate and feasible for this study as we could look at the average HCU per person-year over an extended period of time at the

population level and establish a temporal association between arthritis, mood disorders, and HCU in cancer patients. Although there was some misclassification of exposure as described above, the large sample size, and accounting for the time of development of mood disorders and arthritis provided some suggestions of the impact of these conditions on the HCU of cancer patients. However, a prospective cohort study with the cancer patients diagnosed between a specified period and following them for a substantial duration while taking into account the actual time of diagnosis of mood disorders and arthritis will allow establishing a stronger causal relationship between the chronic conditions, namely arthritis, mood disorders, and health care utilization.

Chapter 7: Conclusion/ Implication/ Future Research

The findings of this population-based study demonstrated that arthritis was not associated significantly with mood disorders in cancer patients in Ontario, rather the number of chronic conditions significantly increased the risk of developing mood disorders. The study also showed that arthritis and mood disorders increased HCU in cancer patients and mood disorders had a more profound impact. Arthritis alone increased only ED visits per person-year while decreasing hospitalization. On the contrary, mood disorders increased both hospitalization and ED visits per person-year. The impact of arthritis and mood disorders on the HCU of cancer patients was most in the absence of any other comorbidities.

MMB is common among cancer patients and around 75% of the patients in Ontario had at least one co-occurring condition (Koné Pefoyo et al., 2015). Addressing MMB in cancer patients is the key to decrease the risk of developing psychological conditions including mood disorders. Depression plays an important role in cancer treatment and outcome. It leads to decreased survival, complicacy in cancer management, and lower quality of life. Identifying cancer patients more prone to develop depression and early screening for the condition will improve cancer management and outcome. Moreover, mood disorders and arthritis increased HCU in cancer patients posing a burden to the health care system. If patients with mood disorders are detected early in the course of the disease, the management of their condition will be less resource-oriented.

Appropriate care management in cancer patients is crucial and is challenged by psychiatric disorders. We identified the combined effect of arthritis and mood disorders on increasing hospitalizations or emergency visits among cancer patients. It is a challenge for the health care system to accommodate complex cancer patients with varied patterns of comorbidities. Identifying the impact of arthritis/mood disorders clusters within each multimorbidity level will help in approaching patients with higher health care needs.

Our study found no increased risk of mood disorders associated with arthritis in cancer patients. However, other chronic conditions may increase the risk of mood disorders in these patients. Future research should be oriented to find out the comorbidities having the highest impact on the mental health of cancer patients. Research regarding individual chronic conditions, MMB, and cancer outcomes like survival and management should be encouraged. We found that the combination of arthritis and mood disorders increased HCU in cancer patients. There should be other clusters of chronic conditions impacting HCU in cancer patients. The future endeavor can be made to identify the disease clusters withing each MMB level causing the highest HCU in order to enable the health care system to optimally deliver health care for the complex cancer patients.

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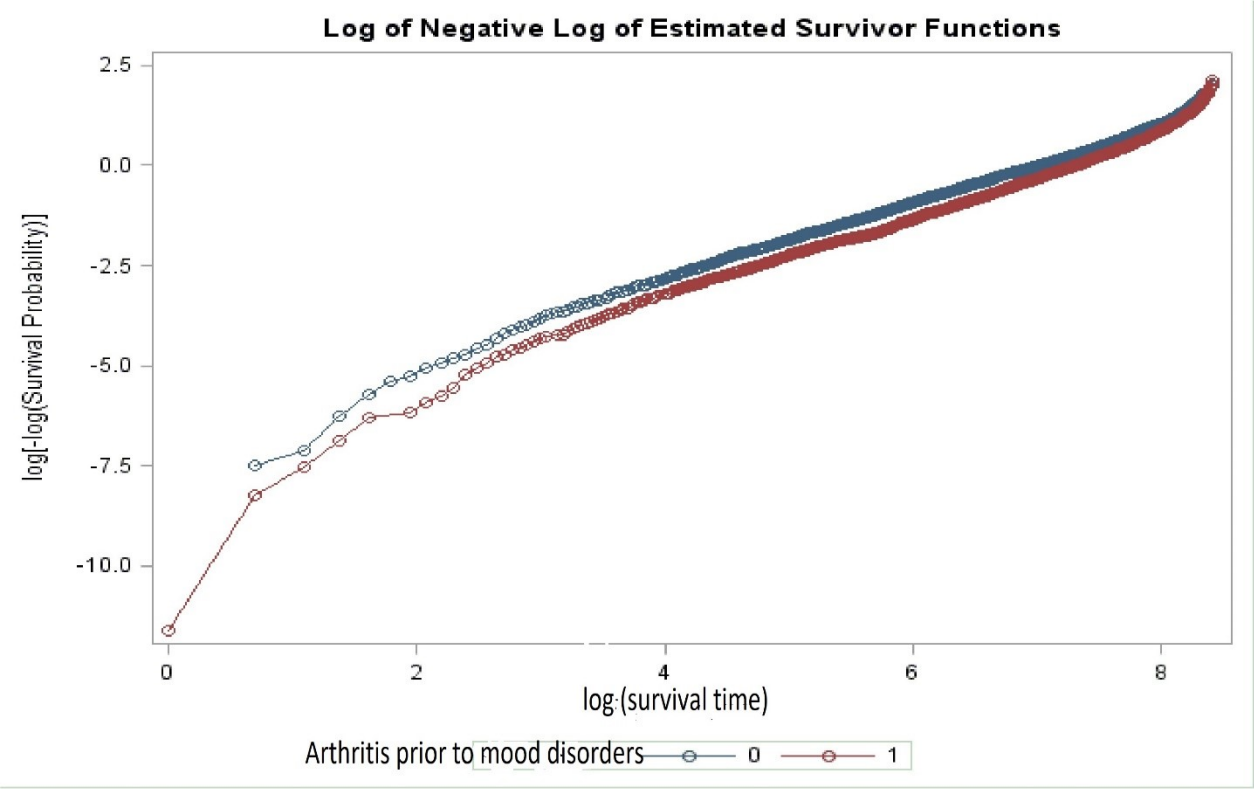
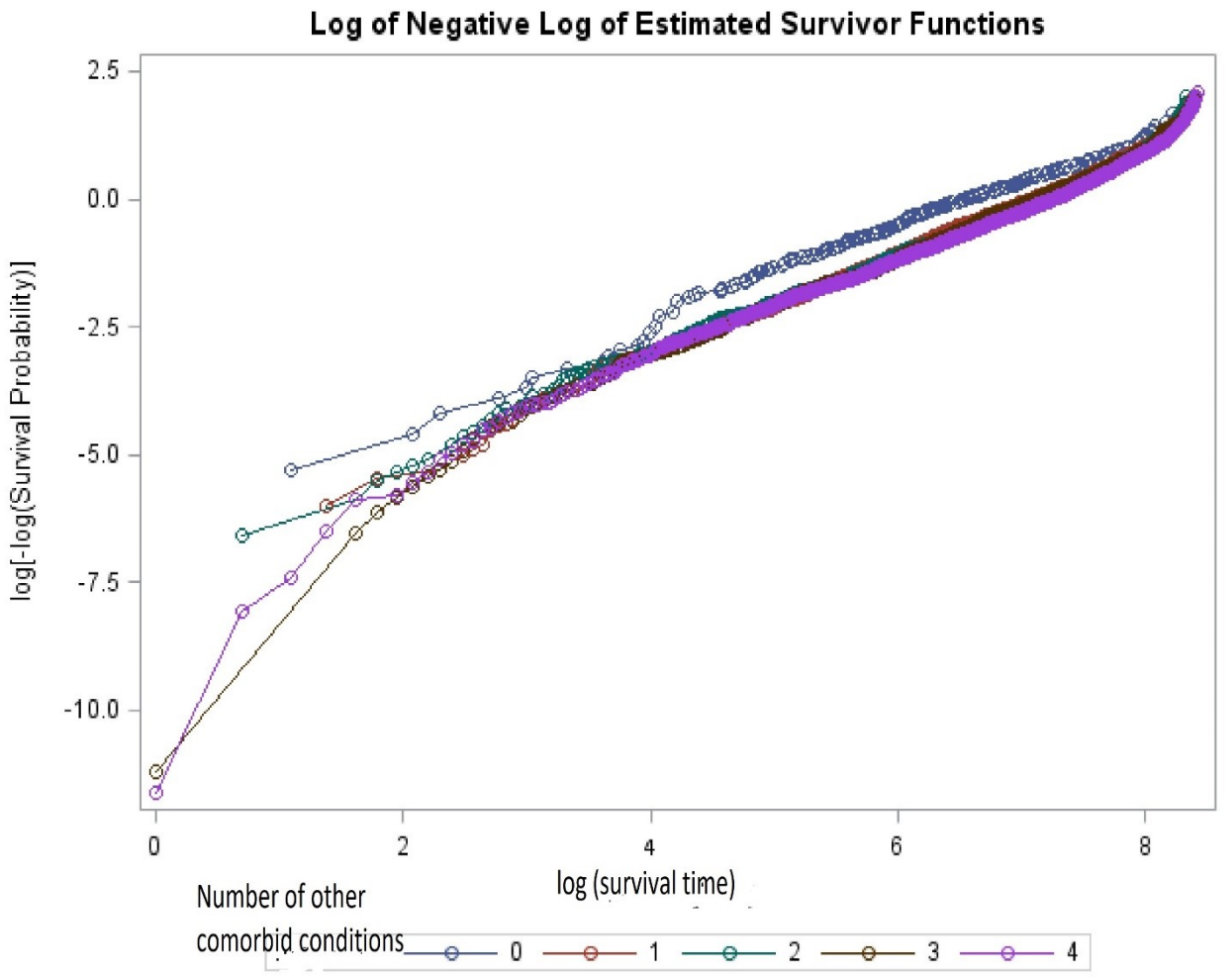
Appendices

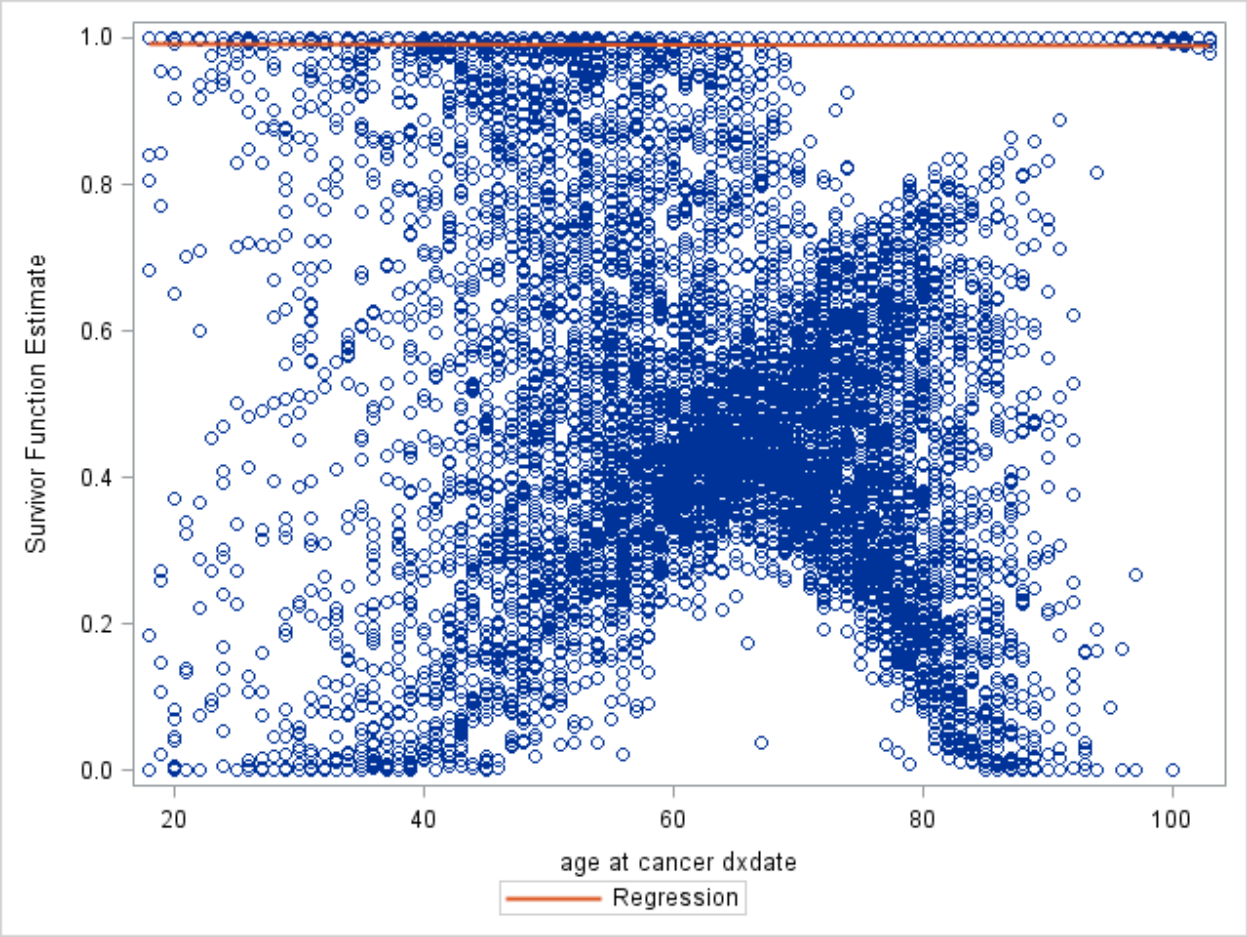
Checking Proportionality of the Main Predictor (Arthritis Prior to Mood Disorders)



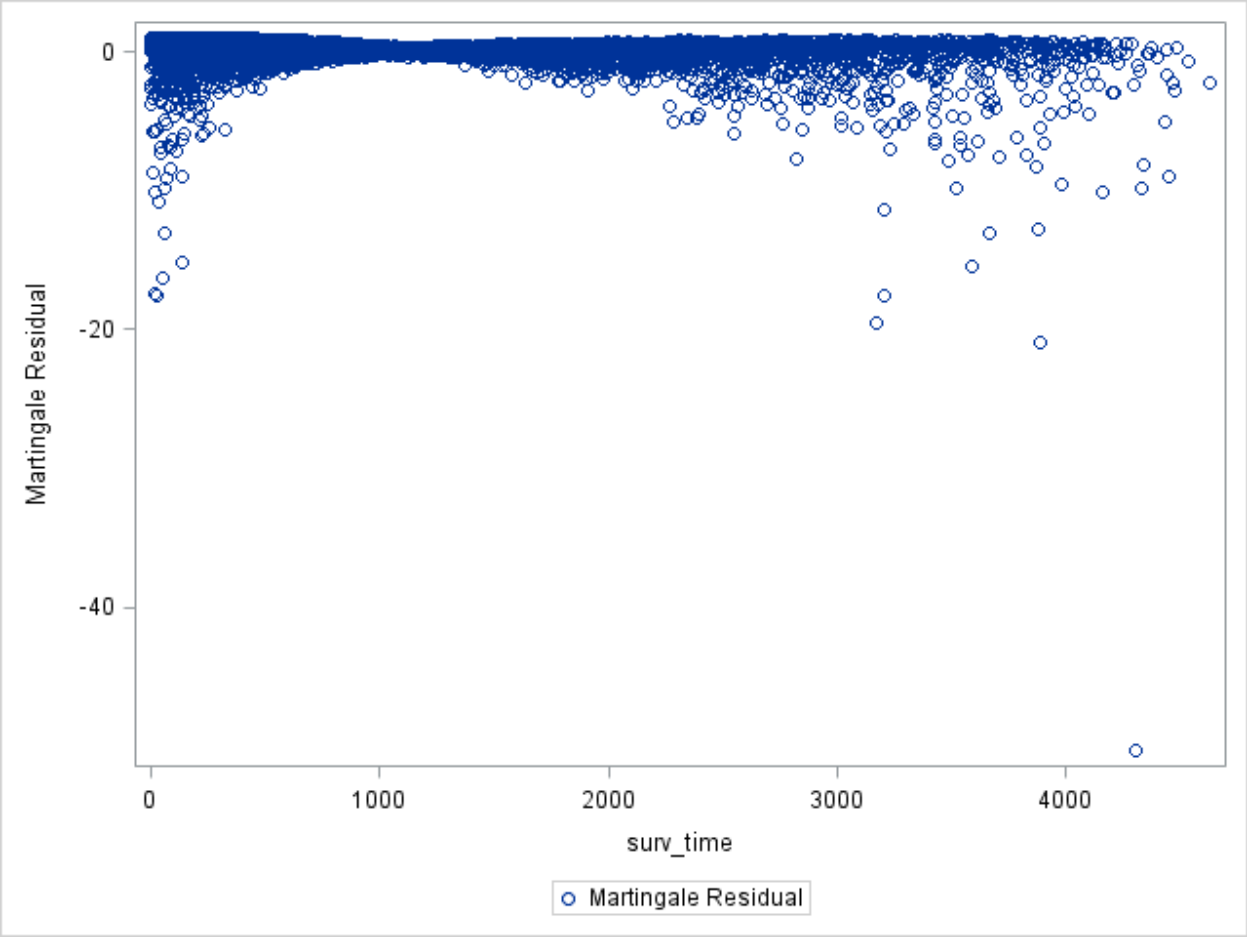
Checking Proportionality of Multimorbidity Levels



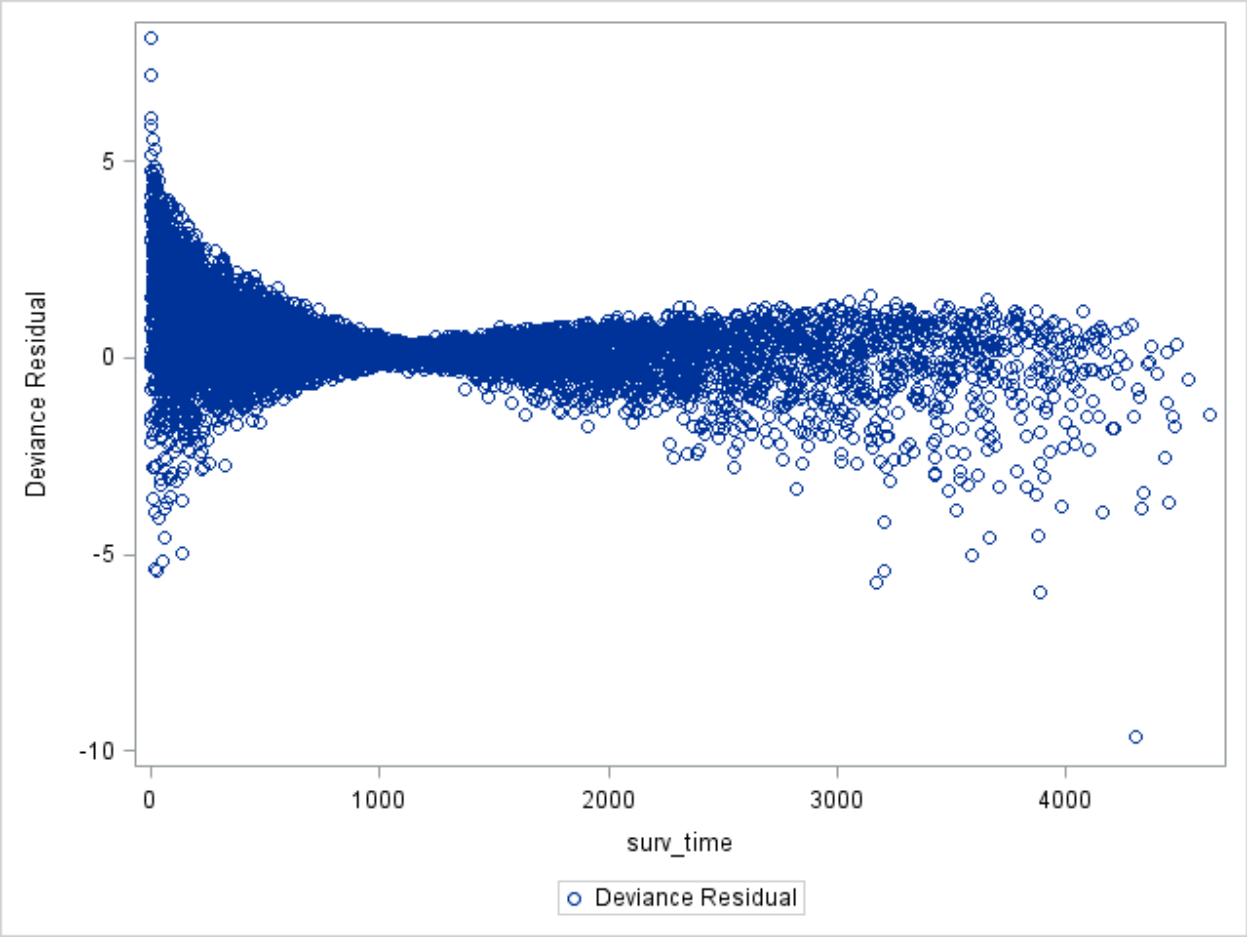
Regression of Continuous Variables with Survival Function



The plot of Martingale Residuals for the Cox Model



The plot of Deviance Residuals for the Cox Model



Model Diagnostic for Negative Binomial Model Showing the Adjusted Impact of Mood Disorders and Arthritis on the Average Annual Hospitalizations of Cancer Patients Including the Interaction Between Cancer and Multimorbidity

Criteria For Assessing Goodness Of Fit			
Criterion	DF	Value	Value/DF
Deviance	45E4	292838.3925	0.6543
Scaled Deviance	45E4	292838.3925	0.6543
Pearson Chi-Square	45E4	457534.5635	1.0223
Scaled Pearson X2	45E4	457534.5635	1.0223
Log Likelihood		-356063.1591	
Full Log Likelihood		-410172.5910	
AIC (smaller is better)		820485.1821	
AICC (smaller is better)		820485.2043	
BIC (smaller is better)		821256.0001	

Model Diagnostic for Negative Binomial Model Showing the Adjusted Impact of Mood Disorders and Arthritis on the Average Annual ED Visits of Cancer Patients Including the Interaction Between Cancer and Multimorbidity

Criteria For Assessing Goodness Of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	45E4	325038.1235	0.7263
Scaled Deviance	45E4	325038.1235	0.7263
Pearson Chi-Square	45E4	594404.4494	1.3281
Scaled Pearson X2	45E4	594404.4494	1.3281
Log Likelihood		-375710.6651	
Full Log Likelihood		-487626.0920	
AIC (smaller is better)		975392.1840	
AICC (smaller is better)		975392.2062	
BIC (smaller is better)		976163.0020	