Impacts of Depression and its Management on the Survival of Cancer Patients With and Without

Other Chronic Diseases

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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.

IMPACTS OF DEPRESSION AND ITS MANAGEMENT ON CANCER SURVIVAL

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Abstract

Objectives: The first part of this study aims to assess the impact of major depressive disorder (MDD) on cancer survival and to determine whether the impact is modified by the number of other comorbidities in a patient. The second part evaluates the impact of adequate antidepressant refill (AAR) on the survival of older cancer patients with MDD.

Methods: The study used a retrospective cohort design and conducted a population-based study on all adult cancer patients diagnosed in Ontario between 2003 and 2013. The cohort was followed until 2018. Patients who had a hospital discharge diagnosis of MDD before or during the study period were identified as having depression. For the second part of the study, data on a subset of patients who were ≥ 65 years old at the time of cancer diagnosis and had MDD were analysed. Fifteen chronic conditions were included for calculating the number of comorbidities excluding MDD. Survival analysis was performed using Cox proportional hazards regression.

Results: Among the 453,012 adults diagnosed with cancer, 2% had a hospital diagnosis of MDD. Those who had MDD had a higher risk of mortality (adjusted hazard ratio (aHR) 1.58; 95% confidence interval (CI) 1.54-1.63) than those without MDD. In patients with MDD, those with 0-1 comorbidities had 2.55 times (aHR 2.55; 95% CI 2.31-2.81), those with 2-3 comorbidities had 1.85 times (aHR 1.85; 95% CI 1.75-1.95), and those with ≥ 4 comorbidities had 1.44 times (aHR 1.44; 95% CI 1.40-1.49) higher risk of death compared to patients without MDD with similar levels of multimorbidity. There were 4,708 patients who were ≥ 65 years old and had MDD. Among patients whose MDD was diagnosed after cancer (N=3,183 (67.6%)), AAR was associated with a lower mortality risk (aHR 0.51; 95% CI 0.47-0.55).

Conclusion: Cancer patients without MDD survive longer than those with MDD. Older patients with MDD diagnosed after cancer are likely to survive longer if they receive AAR.

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Overview of Thesis Content

This thesis is organized into seven chapters. The first chapter provides a general introduction of the topics of this research; depression, multimorbidity, and cancer survival. The second chapter is a literature review synthesizing what is known about the study topics. The third chapter provides a thesis overview which outlines the study objectives and hypotheses, approach to the thesis, and ethical considerations. Chapters 4 and 5 are the publishable manuscripts. Chapter 4 addresses the first two objectives, i.e., determining whether MDD has an impact on the survival of cancer patients and whether number of other comorbidities modifies this impact. Chapter 5 addresses the third objective, i.e., evaluating whether adequate antidepressant refill has an impact on the survival of cancer patients with MDD. The sixth chapter is a general discussion of the overall findings of the study, their epidemiological implications, and the strengths and limitations of the study. Chapter 7, conclusions, is the final chapter and summarizes the study findings and their implications and suggests directions for future research.

List of Abbreviations

AAR – Adequate Antidepressant Refill

aHR – adjusted Hazard Ratio

CI – Confidence Interval

DAD – Discharge Abstract Database

HR – Hazard Ratio

HRQoL – Health-Related Quality of Life

ICES – Institute for Clinical Evaluative Sciences

IDAVE – ICES Data & Analytic Virtual Environment

MDD – Major Depressive Disorder

NACRS – National Ambulatory Care Reporting System

OCR – Ontario Cancer Registry

ODB – Ontario Drug Benefit

OHIP – Ontario Health Insurance Plan

ON-Marg – Ontario Marginalization Index

Ref – Reference category

RPDB – Registered Persons Database

Chapter 1: Introduction

Impacts of Depression and its Management on the Survival of Cancer Patients With and

Without Other Chronic Diseases

Cancer is ranked first among the leading causes of death in Canada (Statistics Canada, 2018a). Almost one in two Canadians will have cancer in their lifetime and it will be the cause of death for one in four Canadians (Canadian Cancer Society, 2019). These statistics are similar for the province of Ontario where there were more than 90,000 newly diagnosed cases of cancer and 30,000 deaths due to cancer in 2018 (Cancer Care Ontario, 2018). It is estimated that the five-year survival rate for all cancers combined for Canadians is 60% (Canadian Cancer Society, 2019).

The risk for cancer increases with age, with nearly 90% of patients receiving a cancer diagnosis after 50 years of age (Canadian Cancer Society, 2019). Because older age is associated with increased prevalence of chronic diseases, patients with cancer are also likely to have other chronic diseases. Modifiable risk factors for many cancers are also risk factors for other chronic diseases, including tobacco, alcohol, overweight/obesity, poor-quality diet, and inadequate physical activity (World Health Organization, n.d.). Cancer patients are more likely to have co-existing medical conditions (i.e., comorbidities) than people with no diagnosis of cancer (Ng et al., 2018).

Symptoms of comorbid conditions can mask the symptoms of cancer and cause delay in cancer diagnosis, which can negatively affect survival (O'Rourke et al., 2008). However, it has also been suggested that comorbidities may be associated with frequent health system encounters, which can lead to earlier detection of cancer (Iachina et al., 2014). Comorbidities can predispose cancer patients to poorer outcomes such as surgical complications, increased length of hospital stay, and increased mortality (Chaudhary et al., 2013; Dehal et al., 2013; Dolan et al.,

2013; Genther & Gourin, 2015). The severity of comorbidities such as heart disease and chronic

obstructive pulmonary disease (COPD) can decrease the survival of cancer patients (Iachina et

al., 2014). Many chronic conditions including hypertension, heart disease, diabetes, and high

cholesterol are common in cancer patients (Sarfati et al., 2016). Depression, with a prevalence of

6.8%, is the most common psychiatric condition among advanced cancer patients (Kadan-Lottick

et al., 2005).

Depression affects cancer patients more than the general population (Hong & Tian,

2014a; Watts et al., 2015). Chronic diseases and cancer can both increase the risk of developing

depression, as depression can be triggered by situations causing feelings of hopelessness and

helplessness (Halberstadt et al., 1984). Among cancer patients, those who have had a past history

of depression or who were undergoing treatment for depression had increased depression scores

over a two-year follow-up period than those with no history of depression (Stafford et al., 2016).

Even cancer survivors who have been cancer-free for five years or more have high levels of

depression (Muzzatti et al., 2017). Depression can make cancer care challenging due to poor

treatment adherence (Hooper et al., 2016; Moraes & Casseb, 2017) and engagement in unhealthy

behaviours (Barros et al., 2017). Depression is associated with poor quality of life (K. H. Hwang,

Cho, & Yoo, 2016; Shakeri et al., 2016) and poor prognosis/outcomes such as mortality in

cancer patients (Kanani et al., 2016; Low et al., 2016). However, proper screening for, and

treatment of depression is cost effective and increases quality-adjusted life years in cancer

patients (Duarte et al., 2015; S. Walker et al., 2014).

Although Canada has universal health care funded through the income tax system

(Ontario, 2020a) that pays for basic health care for all residents, Canadians' mental health needs,

such as need for information regarding mental health conditions and treatments/services,

medication, counselling, and other mental health services are frequently not met (Sunderland & Findlay, 2013). Many parts of Canada have shortages of mental health providers (Anderssen, 2020). In 2012, 12.2% Canadians had unmet mental health needs and 21.1% had partially met mental health care needs (Sunderland & Findlay, 2013). Those who had one or more chronic physical conditions were more likely to have mental health care needs than those who did not have any chronic diseases; however, those who had chronic physical diseases were likely to have their mental health needs taken care of by receiving information, medication, counselling, or other mental health services (Sunderland & Findlay, 2013). Only 50% of Canadians with a major depressive episode received adequate treatment (received antidepressants or visited a health care provider at least six times a year for mental health reasons) in 2012 (Patten et al., 2016).

The high prevalence of depression and other comorbidities in cancer patients and the mixed evidence about the impact on depression on cancer survival leads to the question how depression and its management influence cancer survival among Canadians, especially given the shortcomings of the Canadian health system in providing mental health care. Even though there have been studies examining the effect of depression and comorbidities separately on the survival of cancer patients, what remains unknown is the combined effect of depression and other comorbidities on cancer survival. This study examines whether depression has an impact on the survival of cancer patients in Ontario and whether this effect is modified by the presence of other comorbidities. The study will also assess whether Ontario Health Insurance Plan (OHIP)-covered treatment for depression (i.e., pharmacotherapy) has an impact on the survival of cancer patients with depression.

Chapter 2: Literature Review

This study aims to evaluate the impact of depression on cancer survival in the context of multimorbidity (co-occurrence of more than one chronic disease in a person) and determine whether adequate antidepressant use has an impact on the survival of cancer patients with depression. The existing literature was searched for studies of outcomes in cancer patients, especially in the context of multimorbidity and depression. Reports and peer-reviewed publications that examined the prevalence of multimorbidity and depression, and their impact on the quality of life and survival in cancer patients, were included in the review. Search was conducted in PubMed using combinations of the following keywords: comorbid*, "Comorbidity"[Mesh], "Multimorbidity"[Mesh], surviv*, "Mortality"[Mesh], "Survival"[Mesh], depress*, "Depressive Disorder"[Mesh], "Depression"[Mesh], malignan*, cancer*, "Neoplasms"[Mesh], and antidepressant*. In what follows, I present the results of the literature review to provide a brief background on the topics of this study. It is divided into the following sections: cancer, multimorbidity in cancer patients, depression in cancer patients, possible mechanisms by which depression and other comorbidities affect cancer survival, and antidepressant therapy in cancer patients.

2.1 Cancer

Cancer results from uncontrolled division of abnormal cells which can also invade and spread to other parts of the body (National Cancer Institute, n.d.). Internationally, around 17 million new cases of cancer were diagnosed in 2018 (Cancer Research UK, n.d.). In Canada, there were 206,200 newly diagnosed cancer patients in 2017 (Canadian Cancer Society, 2017). In 2009, 2.4% of Canadians who were alive have had a diagnosis of cancer in the preceding 10 years (Canadian Cancer Society, 2017). Cancer was the main cause of premature mortality in Canada, as the years of potential life lost was the highest for cancer than all other causes of

premature death (Canadian Cancer Society, 2017). Among all health conditions, cancer had the highest cost of productivity loss due to premature death in Canada in 2010 (The Public Health Agency of Canada., 2017). Health care costs in Canada associated with cancer was $7.5 billion in 2012 (de Oliveira et al., 2018).

The most common cancers in Canada are breast, lung and bronchus, prostate, colorectal, and bladder cancers, which account for more than 50% of the newly diagnosed cancers (Statistics Canada, 2019). Half of the deaths due to cancer in Ontario are attributable to lung, colorectal, female breast, and pancreatic cancers, with lung cancer accounting for almost one-fourth of all cancer deaths (Cancer Care Ontario, 2018). However, improved treatment and routine screening have resulted in improved survival rates for breast, prostate, and colorectal cancers (Cancer Care Ontario, 2016).

2.1.1 Cancer Survival

Multiple clinical and sociodemographic factors can impact cancer survival. Patient survival rates vary by cancer type. For example, the five-year survival rate for lung cancer is only 17% while it is 95% for prostate cancer (Canadian Cancer Statistics Advisory Committee, 2018). Diagnosing cancer at its earlier stages can result in better survival rates (Canadian Cancer Statistics Advisory Committee, 2018). Non-small cell lung cancer, which is the most common type of lung cancer in Canada, has a five-year survival rate of 60% if diagnosed in the localized stage, whereas if diagnosed after spreading to distant organs, the five-year survival rate is as low as 6% (American Cancer Society, 2019a). Five-year survival rates for breast cancer and cancers of colon and rectum are around 99% and 90% respectively, if diagnosed at localized stage, and 27% and 15% respectively, if diagnosed after distant spread (American Cancer Society, 2019b, 2019c).

Other factors that influence cancer survival are demographics and socioeconomic status. Increasing age is a factor associated with poorer cancer survival (Sugiura et al., 2017; S. F. Wong et al., 2016), although the relationship can change according to the type of cancer. For example, breast cancer patients diagnosed before age 35 (Wei et al., 2013) and prostate cancer patients diagnosed between ages 40 and 44 (Merrill & Bird, 2002) were found to have poorer survival than those who were diagnosed at later ages. Males are reported to have generally poorer cancer survival rates than females (Ellison, 2016; Kinoshita et al., 2017; Radkiewicz et al., 2017). This can be due to various factors such as women giving more attention to their bodies, leading to earlier diagnosis and better treatment; biological and hormonal factors that favour survival in women; men having more exposure to cancer risk factors; and the differences in the distribution of cancer sub-sites among men and women (Micheli et al., 1998). Women are also higher users of health care services (Bertakis et al., 2000), which can also favor their survival. Ethnicity also contributes to cancer survival. Asian ethnicity has been found to be associated with better survival than non-Asian ethnicity among cancer patients, likely due to differences in tumor biology, lower smoking prevalence, and higher likelihood of being married or having a partner (J. D. Kim et al., 2017). Immigrants in Canada have lower mortality due to cancer when compared to individuals born in Canada (Cheung et al., 2017).

First Nation adults have lower survival than non-Indigenous Canadians (Withrow et al., 2017), likely due to stage at diagnosis, health behaviours, prevalence of comorbidities, and disparities in screening uptakes (Withrow et al., 2017). Indigenous people living in First Nation communities may have limited access to care (Lavoie et al., 2016). Racial stereotyping can lead to Indigenous patients' health complaints being trivialized and receiving poor quality of care (Browne & Fiske, 2001), which can also impact their disease prognosis. A study in New Zealand

showed that Indigenous cancer patients are less likely to undergo definitive treatment and are likely to have delay in time between diagnosis and treatment (Hill et al., 2010).

Income predicts survival probability in cancer patients and higher income is associated with better survival (Altman et al., 2017; Choi et al., 2016; Singer et al., 2017). Low income might limit access to healthy food which can lead to undernutrition, which in turn can result in low immunity and poor survival (Kau et al., 2011). Low-income patients are likely to forgo care (T. J. Kim et al., 2017), which can also negatively impact cancer survival. In Canada, access to care individuals with higher income had better access to care than those with lower income (Lasser et al., 2006). Patients living in areas which fall under lower income quintiles in Canada have poorer cancer survival than those living in areas with higher income (C. Boyd et al., 1999; McDonald et al., 2014).

Rurality of residence can be associated with increased travel for accessing health care, which can impact the quality of care and treatment adherence of cancer patients resulting in poorer survival. However, there are studies that have shown an advantage in survival among cancer patients who are living in urban areas when compared to those living in rural areas (Zhang et al., 2015), although there are many studies showing that there is no such impact (Canale et al., 2018; J. D. Kim et al., 2018). In Canada, neighbourhoods that are most socioeconomically deprived are also generally situated far from treatment centres, which means that poor people have to travel further to get cancer treatment (B. B. Walker et al., 2017), which is likely to impact their care-seeking behaviour and survival.

2.2 Multimorbidity in Cancer Patients

Multimorbidity is the presence of multiple chronic diseases in the same patient. There are multiple methods of measuring multimorbidity in patients such as Elixhauser Comorbidity Index,

which considers duration of hospital stay hospital costs and mortality and is commonly used in hospitalized patients (Elixhauser et al., 1998), Charlson Comorbidity Index, which is commonly used in cancer patients and uses administrative databases for classifying multimorbidity according to number and severity of diseases, (Charlson et al., 1987); Comorbidity-Polypharmacy Score, which is commonly used in trauma patients and considers number of medications as well as comorbidities (Evans et al., 2011); and number of different diagnoses (Lix et al., 2011).

It has been estimated that 26% of Canadians aged 40 years or more had two or more chronic conditions in 2011/2012 (Feely et al., 2017). Among cancer patients in Ontario, the prevalence of multimorbidity was estimated to be more than 70% in 2009 (Koné Pefoyo et al., 2015). Prevalence of multimorbidity varies according to the type of cancer. For example, one study showed that while the prevalence of at least one comorbidity in lung cancer patients was 53%, it was only 30.5% in prostate cancer patients (Edwards et al., 2014). Among cancer patients who are 65 years or older, the prevalence of comorbidities can be as high as 90% (Williams et al., 2018). Further, the diagnosis of cancer could lead to the diagnosis of other conditions because frequent encounters with the health care system following cancer diagnosis can facilitate the detection of previously undiagnosed conditions.

Sociodemographic factors including sex, ethnicity, and income influence multimorbidity (Agborsangaya et al., 2012). Females have increased risk of multimorbidity compared to males in all age groups (Agborsangaya et al., 2012). Contributing factors could include greater susceptibility of females to some conditions such as autoimmune diseases (Hayter & Cook, 2012). In general, females live longer than males, which also makes them more likely to have multiple chronic diseases. When compared to Whites, Asians have lower risk for multimorbidity

while Blacks have a higher risk (St Sauver et al., 2015). Risk of multimorbidity is inversely related to income (Agborsangaya et al., 2012).

2.2.1 Multimorbidity and Cancer Survival

Multimorbidity is associated with increased mortality in cancer, regardless of the type of cancer (Parés-Badell et al., 2017; Patel et al., 2017; Phillips et al., 2017). Among the studies on multimorbidity and survival in cancer patients, some have included only specific cancers (Phillips et al., 2017; Patel et al., 2017) whereas others have included all types of cancers (Lee et al., 2017). High degree of multimorbidity has been found to be associated with higher risk for death in epithelial ovarian cancer (Phillips et al., 2017), metastatic renal cell carcinoma (Patel et al., 2017), and breast, lung and colorectal cancers (Parés-Badell et al., 2017). Higher values in comorbidity scores such as Charlson comorbidity index and Cumulative Illness Rating Scale-Geriatric, calculated by taking into account the comorbidities and their severity in a patient, have a negative impact on cancer survival (Lee et al., 2017; Matthes et al., 2018; Phillips et al., 2017). Multiple health care professionals are involved in taking care of each cancer patient, potentially including physicians, nurses, pharmacists, dieticians, psychologists, etc. (Canadian Cancer Society, n.d.). Physicians who specialize in specific areas such as medical oncologists, radiation oncologists, surgical oncologists, pathologists, anaesthesiologists, and the family physician take part in providing care to cancer patients as required (Canadian Cancer Society, n.d.). If a cancer patient has other chronic conditions, which also require ongoing management, they need services from multiple physicians and other health care professionals. For example, a patient with cancer and rheumatoid arthritis needs an oncologist and a rheumatologist work closely for optimization of care since the medicines for rheumatoid arthritis can cause immunosuppression (Zogala et al., 2017). Cancer patients with diabetes require individualized care by a multidisciplinary team

consisting of oncologists and diabetes specialists (Jacob & Chowdhury, 2015). When multiple disciplines/specialities are involved in a patient's care, care coordination can be challenging, especially when the providers are located in different communities as can be the case for rural patients. Hence, cancer care can be complicated by multimorbidity.

2.2.2 Common Comorbidities in Cancer

Frequently reported comorbidities in cancer patients include hypertension, coronary heart disease, myocardial infarction, stroke, COPD, peptic ulcer, diabetes, renal insufficiency, liver insufficiency, and arthritis (Edwards et al., 2014; C. Ko & Chaudhry, 2002). Multimorbidity is particularly associated with higher risk for depression. When compared to people with no chronic physical conditions, having a chronic physical condition increases the risk for depression by two times and having two or more chronic physical conditions increases the risk by three times (Read et al., 2017).

2.3 Depression in Cancer Patients

Depression is a common mental health condition in which the affected person loses interest in activities previously enjoyed and experiences sadness and worthlessness for longer periods of time than what is expected in grieving (American Psychiatric Association, 2013). The annual prevalence of major depression in Canada is around 5% (Patten et al., 2016). Cancer patients have higher prevalence of depression than the rest of the population (Mols et al., 2018). A systematic review by Walker et al. (2013) found that the prevalence of depression ranged from 5% to 16% in cancer patients receiving outpatient care whereas it was as high as 7% to 49% in cancer patients receiving palliative treatment.

Although females are more likely to have depression than males (Knoll & MacLennan, 2017), it may not always be the case for cancer patients. For example, among colorectal cancer

patients, one study showed that males have higher odds for depression than females (Mols et al., 2018) while another study showed higher odds in females (Clark et al., 2016). Among lung cancer patients, females were found to be more likely to have depression than males (Hung et al., 2017). Another factor that contributes to depression in cancer patients is age, although the pattern may change according to cancer type. Among colorectal patients, older age was found to be associated with higher odds of depression (Mols et al., 2018), whereas among breast cancer (Cvetković & Nenadović, 2016) and lung cancer (Hung et al., 2017) patients, younger age was associated with higher odds of severe depression. Lower socioeconomic status, non-White ethnicity (Clark et al., 2016), and immigrant status (Butow et al., 2013) are also associated with higher likelihood for depression among cancer patients. Stage of cancer and presence of comorbidities also contribute to depression in cancer patients (Clark et al., 2016).

Physical symptoms such as pain (Hong & Tian, 2014) and impairment in activities of daily living (Clark et al., 2016; Hong & Tian, 2014) can increase the risk of depression among cancer patients. At the same time, not everyone who receives a cancer diagnosis becomes depressed. One can experience stress associated with the diagnosis and treatment of cancer; however, symptoms of depression are likely to improve with time following cancer diagnosis (Mols et al., 2018).

2.3.1 Depression and Cancer Survival

There is mixed evidence about the effect of depression on cancer patients' survival, with some studies showing evidence that cancer patients with depression had lower survival than those without depression (Chang et al., 2014; Goodwin et al., 2004; Prasad et al., 2014; Prieto et al., 2005; Shinn et al., 2016) and some studies showing no such effect (Faller & Schmidt, 2004; Nakaya et al., 2006). One study that evaluated the impact of depression or anxiety on survival

showed that among cancer patients, those with anxiety and/or depression had 83% (HR 1.83; 95% CI 1.45-2.31) higher risk for death than those without anxiety and/or depression, although those who contacted a mental health professional in the past year had no excess mortality related to anxiety or depression (Pratt et al., 2016). Another study that examined whether past history of a hospitalization due to severe mental illnesses and comorbidities had an effect on the survival of newly-diagnosed cancer patients showed that cancer patients with history of substance abuse disorder, psychosis, and mood disorders had higher 5-year cancer-specific mortality rates than those without severe mental illnesses (Manderbacka et al., 2017). Studies have failed to find a relationship between distress and survival in certain types of cancers such as ovarian cancer and advanced lung cancer, both of which typically have poor prognosis (de Mol et al., 2017; Minlikeeva et al., 2017). Some studies showed depression was associated with poorer survival at shorter periods of observation, but had no effect on longer term or overall survival (Pirl et al., 2008; Prieto et al., 2005). Pirl et al. (2008) followed 43 patients who were newly diagnosed with non-small cell lung cancer and found that depression was associated with higher risk of mortality at 6 months although overall mortality was not influenced by depression. The maximum survival for the study was 30 months. Prieto et al. (2005) followed 119 hematologic cancer patients and found that mortality at 1 and 3 years was influenced by MDD, whereas 5-year mortality was not impacted by MDD. However, reverse causality cannot be ruled out in short-term survival in cancer patients because patients are likely to develop depression when they know that they have a poor prognosis. Time of depression diagnosis may also influence the impact of depression on cancer survival, as evidenced by studies that showed that diagnosis of depression years before cancer diagnosis was associated with decreased survival (Yang et al., 2018) whereas baseline depression present at the time of diagnosis of cancer failed to show any such effect (Liang et al.,

2017). Several meta-analyses have also shown that depression is associated with decreased cancer survival (Pinquart & Duberstein, 2010; Satin et al., 2009; Wang et al., 2019)

If depression is unrecognized and untreated, it can lead to poorer outcomes in cancer patients (Kissane, 2014). Decreases in depression scores have been found to be associated with improved survival in cancer patients by one study (Giese-Davis et al., 2011), although a recent study by Mulick et al. (2019) did not find any such association.

2.4 Possible Mechanisms by Which Depression and Other Comorbidities Affect Cancer Survival

There are multiple pathways by which multimorbidity and depression can impact cancer survival including delayed cancer diagnosis, nonadherence to treatment and healthy lifestyle, poor quality of life, polypharmacy and related drug interactions, severity of comorbid conditions, and other health care-related factors.

2.4.1 Delayed Diagnosis of Cancer

There are contrasting findings and views about the effect of comorbidities on timely diagnosis of cancer. Although it is likely that patients with chronic diseases have more physician encounters than those without any chronic diseases, which can lead to early diagnosis of cancer, studies have shown that diagnosis of cancer is delayed in patients with comorbidities when compared to patients without comorbidities (Mounce et al., 2017; Whitley et al., 2017; Xiao et al., 2016). One reason may be that since the health care providers are engaged in caring for the already diagnosed conditions in a patient, they fail to recognize the symptoms of cancer and the need for cancer screening. The other reason may be that similarities between the symptoms of cancer and other co-existing conditions in the same patient might prevent early diagnosis of cancer. For example, it has been found that depression is associated with delayed diagnosis of

oesophageal cancer (O'Rourke et al., 2008) because dysphagia, which is a common symptom in oesophageal cancer, is also common in patients with psychiatric illnesses including depression (Regan et al., 2006).

Depression is associated with decreased self-efficacy (Sympa et al., 2018). Hence depressed patients may not undergo screening for cancer and follow treatment recommendations. Depending on symptom severity, depressed patients may not be motivated to seek care for any condition. A study of US military veterans found that depression and trauma-related symptoms were associated with lower likelihood for undergoing prostate cancer screening (Silberbogen et al., 2014).

2.4.2 Adherence to Treatment and Healthy Lifestyle

Depression is a known risk factor for poor adherence to treatment (Hooper et al., 2016; Moraes & Casseb, 2017). Depressed men were found to be less likely to undergo definitive therapy such as surgery and radiation for prostate cancer and had lower survival than nondepressed men (Prasad et al., 2014).

Depression has been identified as one of the factors that can prevent cancer survivors from adhering to physical activity goals (Black et al., 2018; Chipperfield et al., 2013). Depression is associated with higher risk of smoking, recreational drug use (Ruggles et al., 2017), excessive alcohol use, and unhealthy diet (Barros et al., 2017). Sleep disorders are also very common in depressed patients (Nutt et al., 2008), which can also impact quality of life and survival of cancer patients with depression.

Multimorbidity has been found to be associated with premature discontinuation of treatment by breast cancer patients (Nabieva et al., 2018). Cancer diagnosis has been found to lead to decreased adherence to the comorbidity medications (Banegas et al., 2018), which can

result in worsening of comorbid conditions resulting in poorer survival. A study in China found that multimorbidity is associated with poorer adherence to cardiovascular medications (M. C. S. Wong et al., 2014).

2.4.3 Quality of Life

Depression and comorbidities are associated with higher likelihood of fatigue in cancer survivors (Hwang I. C. et al., 2014; J. M. Jones et al., 2016; Storey et al., 2012), which can also be a barrier for adapting healthier lifestyles (Breedveld-Peters et al., 2018). Colorectal cancer patients with depression had higher rates of increase in fatigue and pain and decrease in physical, emotional, cognitive, and social functioning after five years following surgery than patients without depression (Cummings et al., 2018; Mols et al., 2018). Cancer-related fatigue can persist many years after treatment and is associated with increased disability (J. M. Jones et al., 2016). Long-term persistence of fatigue in breast cancer patients has been linked to pre-existing depression (Schmidt et al., 2015). Fatigue can prevent cancer patients from being physically active and hence lead to poorer survival. Depression is also associated with poor health related quality of life (HRQoL) even after many years following cancer treatment (Kenzik et al., 2015; Schoormans et al., 2015) and poor HRQoL is associated with shorter survival (Kenzik et al., 2015).

2.4.4 Polypharmacy

Multimorbidity frequently requires polypharmacy, which can result in drug interactions in cancer patients which can also impact their survival. One study showed that around 58% of cancer patients had at least one potential drug interaction (van Leeuwen et al., 2011). A study conducted among cancer patients undergoing only palliative treatment showed the prevalence of drug interactions to be 31%, of which 59% was of moderate severity (Riechelmann et al., 2008).

Among older cancer patients, studies have shown varying prevalence of severe drug interactions ranging from 35% (Alkan et al., 2017) to more than 60% (Nightingale et al., 2018).

2.4.5 Severity of Comorbidities

Cancer patients with multimorbidity are at risk for death due to cancer as well as risk of death from other chronic diseases depending on the severity of the conditions. If cancer is diagnosed at an earlier stage (i.e., local or regional stages), they are likely to die due to diseases other than cancer, especially in cancers with good prognosis (Edwards et al., 2014). If cancer is diagnosed at a later stage (i.e., distant stage) their cause of death is likely to be cancer. Increased comorbidity scores are related to higher risk for noncancer-related deaths among cancer patients, especially in those diagnosed at an earlier stage (Edwards et al., 2014). Cancer patients with depression are four times more likely to have suicidal ideations than those without depression (Tang et al., 2016).

2.4.6 Health Care Factors

A study done in the United States of America by Druss et al. (2008) found that patients with untreated depression are less likely to have a usual source of health care than persons without depression. Untreated depression patients are less likely to have had a health care visit in a two-year period or receive preventive health services including influenza vaccine, blood pressure check, and screening for breast, cervical and colorectal cancers than non-depressed individuals (Druss et al., 2008). Failure to receive preventive health services can lead to delayed diagnosis of diseases and thus impact survival of depressed patients. Patients who were treated for depression in speciality care had a high likelihood of reporting that their primary care physician did not inquire about their medications that were prescribed by other providers (Druss et al., 2008). Physical complaints of patients with mental illnesses may not be taken seriously or

attributed to their mental illness (Hamilton et al., 2016; S. Jones et al., 2008). As a result, they may not receive timely and appropriate treatment for their physical comorbidities (Atzema et al., 2011), which can impact their survival.

Multimorbid patients receive care from multiple sources including primary care physicians, specialists, rehabilitation facilities, inpatient and outpatient hospital settings, and counselling services, which are separate entities and the services provided by them are specific for particular conditions. The siloed health care systems can make it difficult for patients to transition among the care providers (C. M. Boyd & Fortin, 2010). Time constraints of health care providers, delay in updating medications and discharge summaries, and unclear medical records can adversely affect the quality of care received by patients when multiple specialities and providers are involved in their care (Mc Namara et al., 2017), impacting survival.

2.5 Antidepressant Therapy in Cancer Patients

Antidepressants are recommended as the first line of treatment for moderate to severe depression in cancer patients (Li et al., 2016). In oncology, antidepressants are used for treating multiple symptoms in addition to depression (Grassi et al., 2018). It is used for the management of pain, hot flashes, nausea/vomiting, poor appetite, and fatigue in cancer patients (Grassi et al., 2018). Selective serotonin reuptake inhibitors (SSRIs) are considered to the best type of antidepressants for treating depression in cancer patients (Grassi et al., 2018). Other antidepressant categories used in cancer patients include tricyclic antidepressants, monoamine oxidase inhibitors, serotonin antagonist and reuptake inhibitors, selective norepinephrine reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors (Grassi et al., 2018).

On average, it takes one to two weeks of treatment before the patient starts feeling the benefits of antidepressant use (American Psychiatric Association, 2010; National Health Service,

2018) and it may take four to eight weeks to attain the full benefits of a specific dose (American Psychiatric Association, 2010). It is recommended that patient remains on the antidepressant for at least six months following symptom remission (National Health Service, 2018). Most of the newer-generation antidepressants have some adverse effects associated with their usage (Carvalho et al., 2016). They include gastrointestinal symptoms such as nausea and diarrhoea, liver toxicity, cardiovascular symptoms, suicidality, hyponatraemia, sexual dysfunction, osteoporosis, and hyperprolactinaemia (Carvalho et al., 2016). Hence, antidepressants are prescribed to cancer patients only when the benefits outweigh the risks (Li et al., 2016). Certain types of antidepressant medications, such as SSRIs, can lead to worsening of some types of cancers (see below).

Demographic factors associated with antidepressant use include age, sex and ethnicity (Fisch et al., 2015). Being female, non-Hispanic White ethnicity, and older age are associated with higher likelihood for antidepressant usage among cancer patients (Fisch et al., 2015). Cancer patients with comorbidities are more likely to use antidepressants within six months before and after cancer diagnosis than those without comorbidities (Pearson et al., 2015). Cancer patients who are nearing death are also likely to initiate antidepressant therapy (Pearson et al., 2015).

2.5.1 Antidepressant Use and Cancer Survival

Antidepressant use may improve the quality of life of cancer patients with depression (Fisch et al., 2003; Nikbakhsh et al., 2018; Pezzella et al., 2001) and as a result improve their lifestyle and survival. However, one study showed that antidepressant use did not have an effect on the quality of life of cancer patients although the study did not consider the duration of antidepressant use (Vyas et al., 2017). There is some evidence that antidepressant use is

associated with longer survival in lung cancer patients as shown by one study (Zingone et al., 2017), although another study among lung cancer patients showed that antidepressant use, mental health visits, and hospitalizations for depression were associated with higher risk for death (Sullivan et al., 2014).

Treatment of depression using SSRIs was found to be associated with a higher mortality rate in breast cancer patients by one study (Busby et al., 2018) and the investigators suggested that it might be because SSRIs increased prolactin levels (Cowen & Sargent, 1997) which facilitates progression of breast cancer and metastasis (Tworoger & Hankinson, 2008) or because SSRIs reduces the metabolism of tamoxifen (Desmarais & Looper, 2009). A study on ovarian cancer patients also showed that SSRI use is associated with faster disease progression (Christensen et al., 2016). It is likely that if patients diagnosed with breast or ovarian cancer are later diagnosed with depression, they may not receive an antidepressant due to the above facts.

Past studies have examined the impact of depression and multimorbidity on the survival of cancer patients. There was one study that examined the impact of pre-existing mental health disorders on survival and found that the impact varied according to number of comorbidities (Lin et al., 2016). The study included only lung cancer patients who were beneficiaries of the US Military Health System (Lin et al., 2016). There is a paucity of studies at the population level in Canada that looked at the combined effect of depression and presence of other comorbidities on cancer survival. The conflicting results about the relationship between antidepressants and survival in cancer patients and the scarcity of evidence at the population level, especially in Canada, call for more research studying the impact of antidepressant therapy on the survival of cancer patients with depression. The current study tries to address those gaps in research by assessing the impact of depression on the survival of cancer patients in the context of

multimorbidity and the impact of antidepressant therapy on the survival of cancer patients with

depression in Ontario.

Chapter 3: Thesis overview

A review of the literature suggests that depression can have a negative impact on cancer survival, although it is not known how multimorbidity influences the relationship between depression and cancer survival. Also, there is inadequate evidence regarding the impact of antidepressant therapy on the survival of cancer patients with depression. This study aims to address those gaps in research. Understanding the effect of depression on survival can help physicians in decision making regarding management of cancer patients, especially patients with multimorbidity who have complex health care needs. Evidence about the impact of adequate antidepressant use on cancer survival can assist physicians in managing cancer patients with depression efficiently for achieving better outcomes.

3.1 Objectives

The aim of this study is to examine whether the presence of depression and other comorbidities is associated with survival among cancer patients, and whether adequate antidepressant use, defined as taking an antidepressant for 180 days or more (Duhoux et al., 2012), improves survival among cancer patients with depression. The specific research questions that I will investigate are:

1. Does depression influence the survival of cancer patients in Ontario?

2. Does the impact of depression on the survival of cancer patients vary according to the presence of other comorbidities?

3. Does adequate antidepressant use affect the survival of cancer patients with depression with or without other comorbidities?

3.2 Approach to Thesis

A quantitative approach was applied using existing health care administrative data to address the research questions.

The conceptual framework for this study was based on the Andersen's Behavioural Model of Health Services Use (Andersen, 1995). The model was selected because it explains health outcomes as a function of health care utilization; health care needs; and socioeconomic, demographic, and access-to-care factors (Andersen, 1995). According to the model, predisposing factors such as demographics, social characteristics, and health beliefs; enabling resources such as income, health insurance and other access-to-care indicators; and need for health care as perceived by the individual or evaluated by a professional influence health services utilization and, in turn, health outcomes such as patient satisfaction, health status etc. (Andersen, 1995). In this study, we are studying the impact of major depressive disorder (MDD) (exposure) on the survival (outcome) of cancer patients while taking into account some of the demographic and socioeconomic factors, which are the predisposing and enabling factors (confounders), and assessing whether the number of comorbidities (effect modifier) modifies the impact. We are also studying the impact of antidepressant usage on the survival of cancer patients with MDD, while adjusting for the predisposing and enabling factors.

3.3 Hypotheses

This study has two hypotheses that are reflected in the proposed conceptual frameworks (Figures 1 and 2).

Hypothesis #1. MDD has an impact on survival of cancer patients and this impact varies according to the presence of comorbidities, after controlling for sociodemographic and clinical factors (Figure 1).

Figure 1

Hypothesis #1: MDD has an impact on survival of cancer patients and this impact varies

according to the presence of comorbidities, after adjusting for confounders
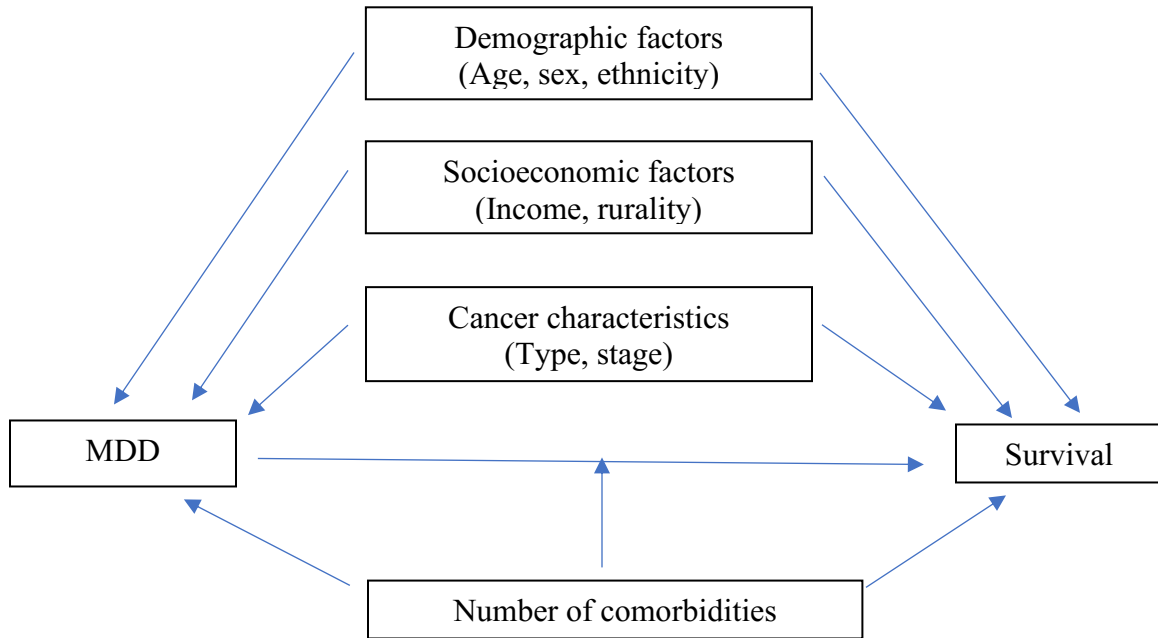
Hypothesis #2. Adequate antidepressant therapy influences the survival of cancer patients with

MDD and time of MDD diagnosis may modify this influence after controlling for

sociodemographic and clinical factors (Figure 2).

Figure 2

Hypothesis #2: Adequate antidepressant therapy influences the survival of cancer patients with

MDD and time of MDD diagnosis may modify this influence, after adjusting for confounders
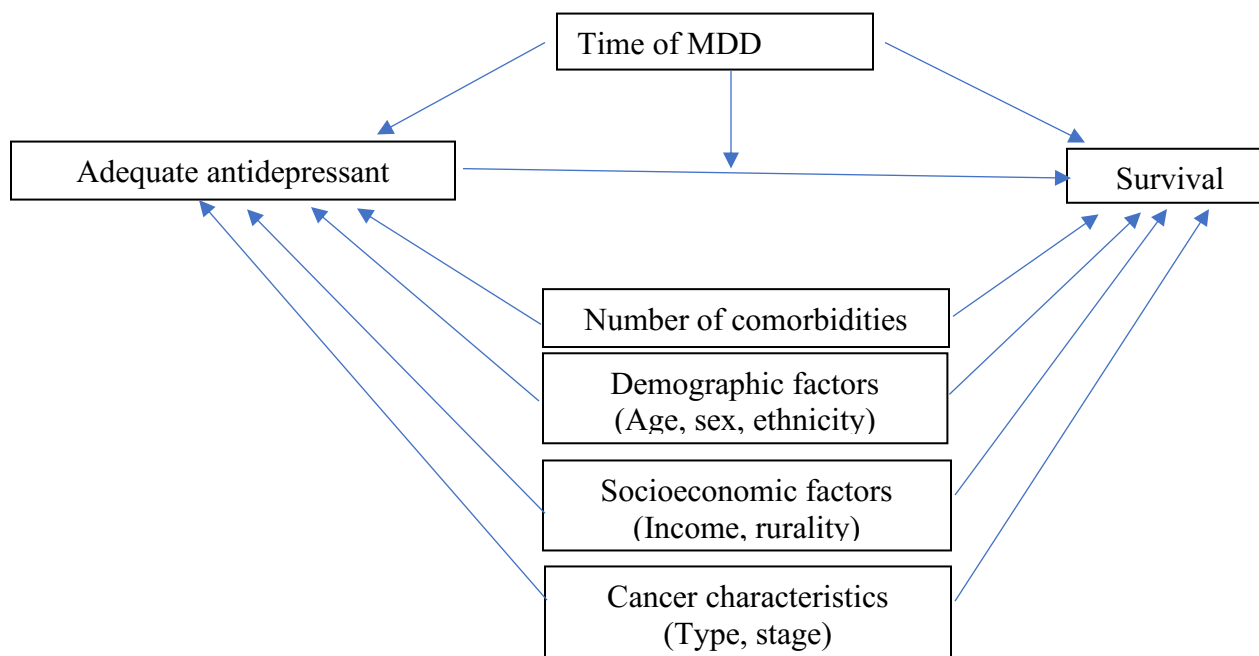
3.4 Study Design and Data Sources

We used a retrospective cohort design with population-based health administrative data available from Institute for Clinical Evaluative Services (ICES) to answer our research questions. The participants were identified from a set of linked provincial health care databases available from the ICES. All Ontario residents, including immigrants after an initial three-month waiting period, are covered by the provincial health insurance program and hence have unique health card numbers. ICES collects personally identifiable health-related data from various sources including physician and hospital records (Institute for Clinical Evaluative Sciences, n.d.). Each

individual in Ontario is assigned a unique ICES code and all personal identifiers are removed from the datasets before they become part of the ICES inventory.

Type of cancer at the time of diagnosis was identified from the Ontario Cancer Registry (OCR) using the ICD-O-3 definition (National Cancer Institute, 2008) from the OCR. The variable for type of cancer was divided into nine categories: breast, colorectal, digestive system except colorectal, female genital, hematological, lung and bronchus, prostate, urinary system, and other. Information on stage of cancer was also available, but for a limited number of cases.

Ontario Marginalization Index (ON-Marg), based on dissemination area and/or census tract data as available, has information regarding deprivation or marginalization according to demographic characteristics including ethnic concentration quintile, higher values of which represent higher concentration of recent immigrants (arrived in Canada in the past 5 years) and visible minorities (Matheson et al., 2018). Vital status (dead or alive), nearest neighbourhood income quintile, and rurality index were obtained from the Registered Persons Database (RPDB). Rurality Index of Ontario scores of 0 to 39 were considered as urban and scores 40 and above were considered rural (Glazier et al., 2012).

Ontario Health Insurance Plan (OHIP) claims database has details about physician visits and Discharge Abstract Database (DAD) has hospital admission data. Time of diagnosis of depression was obtained from the DAD database. The variable time of depression diagnosis has two categories, before cancer diagnosis and after cancer diagnosis. Ontario Drug Benefit claims database (ODB) has information about drug claims by ODB beneficiaries such as drug identification number, quantity dispensed, and dispensing date. Details about the databases used for the study are included in Table 1.

The databases from ICES have been used for past research on multimorbidity in Ontario (Koné Pefoyo et al., 2015; Mondor et al., 2018; Moin et al., 2018). ICES data has been tested for accuracy in identifying chronic conditions such as hypertension (Tu et al., 2007), diabetes (Hux et al., 2002), asthma (Gershon et al., 2009a), chronic obstructive pulmonary disease (Gershon et al., 2009b), and cardiac conditions such as myocardial infarction, congestive heart failure and arrhythmia (Austin et al., 2002). It has been found that the data had sensitivity more than 80% and specificity more than 75% for all of those conditions except congestive heart failure and arrhythmia which had poor sensitivity at 59% and 61% respectively when they were the main reason for hospital stay (Austin et al., 2002).

The health administrative databases at ICES have information about antidepressant use only for those who benefit from the ODB Program. Hence, we examined the effect of antidepressant therapy on the survival of ODB beneficiaries who had both cancer and inpatient diagnosis of major depressive disorder (MDD). All residents of Ontario become eligible for ODB when they become 65 years old (Ontario, 2019). Younger individuals may also be eligible for ODB if they are residing in long-term care homes or homes for specialized care or are beneficiaries of one of the government-funded services including Home care, Ontario Works, Ontario Disability Support Program, Trillium Drug Program, and OHIP+: Children and Youth Pharmacare. More than 4,400 prescription drugs are covered under the ODB program (Ontario, 2019). We did not include the < 65 age group in the analysis for objective #2 because since all residents of that age group are not eligible for ODB, the analysis results may not be generalizable to everyone in that age group.

Table 1

ICES databases used for obtaining data for the study

Database	Description	Variables
Discharge Abstract Database (DAD)	Information on hospitalizations in Ontario. Includes admissions, length of stay and discharges.	Major depressive disorder using the diagnosis codes, date of diagnosis
Ontario Cancer Registry (OCR)	Information on all Ontario residents diagnosed with cancer. Includes date of diagnosis, site of primary cancer and cancer deaths.	Date of diagnosis, age at diagnosis, date of birth, sex, primary cancer site, stage at diagnosis, date of death
Ontario Health Insurance Plan (OHIP) claims database	Information on claims paid for by OHIP. Includes physician visits, hospitalizations and associated diagnosis.	Comorbidities including depression using the diagnostic codes, time of diagnosis
Registered Persons Database (RPDB)	Demographic information for all individuals who have ever had a valid Ontario health card number. Includes age, sex, neighbourhood income and residence.	Neighbourhood income quintile, rurality, date of death
National Ambulatory Care Reporting System (NACRS)	Information on outpatient visits to hospital and community-based ambulatory care. Includes day surgery, outpatient clinics, and emergency departments.	Comorbidities including depression using the diagnostic codes, time of diagnosis
Ontario Drug Benefit (ODB) claims database	Information about drug claims by ODB beneficiaries such as drug	Antidepressant use from DIN, time prescribed, quantity dispensed

	identification number, quantity dispensed, and dispensing date	
Ontario Marginalization Index (ON-Marg)	Information regarding deprivation or marginalization based on residential instability, material deprivation, dependency, and ethnic concentration	Ethnic concentration quintile

3.5 Ethical Considerations

This study was part of a larger research project on multimorbidity and cancer. It was supported by ICES and funded through a team grant from the Ontario Ministry of Health and Long-Term Care. All the researchers involved had valid certificates of completion of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans - Course on Research Ethics (TCPS 2: CORE). Ethics approval was obtained from ICES and Lakehead University Research Ethics Board before obtaining access to data. ICES has a secure user interface, ICES Data and Analytic Services Environment (IDAVE), which provides a virtual desktop infrastructure accessible for the researcher using ICES user credentials. The data remains on IDAVE and the researcher does all analyses using the software provided in the virtual environment. Hence, privacy of the data is ensured by ICES at all times. The data do not contain any identifying information and only aggregated results are released back to the researchers for use outside of the secure IDAVE environment.

Chapter 4: Impact of Depression on the Survival of Cancer patients With and Without

other Comorbidities: A Population-based Retrospective Cohort Study

Abstract

Aim: To evaluate the impact of major depressive disorder (MDD) on cancer survival and to assess whether the number of other comorbidities modifies the impact.

Method: A population-based retrospective cohort study was conducted on all adult cancer patients diagnosed in Ontario between April 2003 and March 2013, who survived at least a year following cancer diagnosis. They were followed until March 2018. Depression was defined as having a hospital discharge diagnosis of MDD before or during the study period. Fifteen chronic conditions were included for calculating number of comorbidities excluding MDD. Survival analysis was performed using Cox proportional hazards regression.

Results: Among the sample (N=453,012; median age at cancer diagnosis 64 years; 50% female), only 2% had MDD diagnosed in hospital. One quarter (25.8%) had 0-1 comorbidities, 38.8% had 2-3 comorbidities, and 35.4% had ≥ 4 comorbidities other than MDD. MDD was associated with a higher risk of mortality (adjusted hazard ratio (aHR) 1.58; 95% confidence interval (CI) 1.54-1.63). The impact of MDD on mortality varied according to the number of other comorbidities. aHR was 2.55 (95% CI 2.31-2.81) for patients with 0-1 comorbidities, 1.85 (95% CI 1.75-1.95) for patients with 2-3 comorbidities, and 1.44 (95% CI 1.40-1.49) for patients with ≥ 4 comorbidities. Stratified analysis by cancer type was performed and showed that there were no substantial differences in the impacts of MDD between most cancer types.

Conclusion: MDD is associated with higher risk of mortality in cancer patients. Impact of MDD on cancer survival varies according to number of comorbidities, and is similar across many cancer types.

Impact of Depression on the Survival of Cancer Patients With and Without Other Chronic Diseases: A Population-based Retrospective Cohort Study

Psychological conditions such as anxiety (Vodermaier et al., 2017) bipolar disorder, and depression (Kanani et al., 2016) can influence cancer survival. On average, 8 to 24% of cancer patients suffer from depression, although the prevalence varies according to type of cancer (Krebber et al., 2014). Depression is associated with delayed cancer diagnosis (O'Rourke et al., 2008) and reduced adherence to treatment recommendations (Hooper et al., 2016; Moraes & Casseb, 2017), diet (Barros et al., 2017) and exercise regimens (Black et al., 2018; Chipperfield et al., 2013), which can all contribute to poor survival. Sleep disorders (Nutt et al., 2008) and low quality of life (Kenzik et al., 2015; Schoormans et al., 2015) associated with depression can also lead to higher mortality among depressed cancer patients.

Besides depression, the high prevalence of multimorbidity (co-occurrence of more than one chronic disease in a person) among cancer patients (Pefoyo et al., 2015) complicates cancer and other disease care. Multiple specialties and management modalities are involved in the treatment of multimorbid patients. Siloed health systems (Boyd & Fortin, 2010) and practical difficulties in effective communication between health care providers (Mc Namara et al., 2017) can impact the quality of care received by multimorbid cancer patients. Severity of comorbidities (Edwards et al., 2014) and polypharmacy and resulting drug interactions (Riechelmann et al., 2008; van Leeuwen et al., 2011) may also result in poor survival in cancer patients with other chronic conditions.

Past studies have shown mixed evidence about the impact of depression on cancer survival (Faller & Schmidt, 2004; Nakaya et al., 2006; Prasad et al., 2014; Prieto et al., 2005) and mostly negative impact of multimorbidity on cancer survival (Parés-Badell et al., 2017; Patel

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et al., 2017; Phillips et al., 2017). However, there is limited evidence on their combined impact (J. Lin et al., 2016), and it is not clear whether the effect of depression is modified by multimorbidity. This study aims to quantify the effect of depression on the survival of cancer patients in Ontario, Canada, and examines whether this effect is modified by the presence of other comorbidities.

Methods

Study Design and Data Sources

A retrospective cohort design was used including population-based health administrative data available from the Institute for Clinical Evaluative Sciences (ICES). Canada has a publicly funded health care system which ensures universal coverage. All residents of Ontario, including immigrants following an initial three-month waiting period, are eligible for the provincial health insurance program and hence have unique health card numbers. ICES is a non-profit research organization (Institute for Clinical Evaluative Sciences, n.d.a) that collects health-related data in Ontario from various sources including physician and hospital records (Institute for Clinical Evaluative Sciences, n.d.b). The provincial health insurance claims databases at ICES have information about all individuals accessing health care in Ontario, Canada. Various databases containing information on the same individual can be linked using the individual's unique ICES code to obtain data regarding inpatient services, outpatient services, and drugs (Institute for Clinical Evaluative Sciences, n.d.b). The databases used for this study include Ontario Cancer Registry, Ontario Marginalization Index, Registered Persons Database, Ontario Health Insurance Plan claims database, Discharge Abstract Database, and National Ambulatory Care Reporting System. Details about the databases are included in Appendix A. This study was approved by the ICES and Lakehead University Research Ethics Board.

Study Population

All adults in Ontario, Canada, aged 18 years or more who were diagnosed with cancer from April 1, 2003 to March 31, 2013 were included in the study and followed until March 31, 2018. Patients who were more than 105 years old and those with invalid health card numbers were excluded. Patients who died within one year of cancer diagnosis were also excluded from the study to minimize reverse causality.

Study Measures

Time of death was identified from the Registered Persons Database to estimate the primary outcome, survival time. Survival time represents time from cancer diagnosis to death or until March 31, 2018, for those still alive at the end of the study.

The main exposure, depression, was defined as having major depressive disorder (MDD) as one of the diagnoses on a patient's discharge summary following hospitalization up to three years before the study index date or at any point during the follow-up period. MDD was identified using the ICD 10 codes F32 (Major depressive disorder, single episode) and F33 (Major depressive disorder, recurrent) in the Discharge Abstract Database. Number of comorbidities excluding depression was included as a potential effect modifier of the impact of depression on cancer survival. Fifteen chronic diseases were included in the study: osteoarthritis, hypertension, asthma, diabetes, chronic coronary syndrome, cardiac arrhythmia, osteoporosis, chronic obstructive pulmonary disease, congestive heart failure, renal failure, dementia, rheumatoid arthritis, stroke, acute myocardial infarction, and other mental disorders (substance use, psychotic illness, anxiety, other mood disorders, stress, or personality disorder). They were selected based on previous research on multimorbidity (Pefoyo et al., 2015). The list of ICD codes used for identifying each condition is provided in Appendix B. Other covariates included

in the analyses are sociodemographic factors such as age at cancer diagnosis, sex, ethnic concentration quintile, neighbourhood income quintile, and rurality of residence and cancer characteristics such as type of cancer, and cancer stage. Ethnic concentration quintile was obtained from Ontario Marginalization Index and higher values represent higher concentration of recent immigrants (arrived in Canada in the past 5 years) and visible minorities (Matheson et al., 2018). Rurality Index of Ontario scores of 0 to 39 were considered as urban and scores 40 and above were considered rural (Glazier et al., 2012).

Analyses

All analyses were performed using the statistical analysis software SAS (SAS Institute, 2013). Chi-square test and ANOVA were conducted to assess the bivariate associations between patients' sociodemographic characteristics (age, sex, ethnicity, income, and rurality), cancer characteristics (type of cancer and stage), MDD, and number of other comorbidities and vital status. Kaplan-Meier estimates and curves were obtained, and log-rank tests performed, for bivariate analysis with survival time.

Multivariate survival analysis was performed using Cox proportional hazards regression to study the adjusted impact of MDD on the risk of death. To investigate whether the impact of depression on cancer survival was modified by number of other comorbidities, interaction between depression and number of comorbidities other than depression was tested. The interaction was statistically significant and hence included in the analyses. Stratified analyses by age group (<65 years and ≥ 65 years) was conducted to compare the impact of MDD on the survival of younger and older cancer patients. Stratified analysis by cancer type was performed to assess whether the impact of MDD on survival varied according to type of cancer.

Results

Descriptive and Bivariate Analyses

The sample included 453,012 patients in Ontario, aged 18 or more, who survived at least one year after cancer diagnosis. On average a patient was in the study for 7.5 years and 37.9% died during the study period. Table 1 shows the characteristics of the whole sample and indicates that mortality is associated with each variable. Only 2% of the sample had a hospital discharge diagnosis of MDD. Among those with MDD, 62.3% were deceased by the study endpoint compared to 37.4% among those without MDD. Multimorbidity was common in the sample with 35.4% having ≥ 4 chronic diseases besides cancer and MDD.

The prevalence of each additional chronic disease is listed in Appendix B. Proportion of deceased patients increased with the number of chronic diseases, from 25.7% among patients with 0 or 1 comorbidity other than MDD to 52.8% among those with ≥ 4 comorbidities.

Table 1

Characteristics of the sample (Cancer patients aged ≥ 18 years who survived at least a year following cancer diagnosis)

Variable	Whole sample[a] (N=453,012)		Alive[b] (N=281,268 (62.1%))		Deceased[b] (N=171,744 (37.9%))		
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*ANOVA p-value*
Number of years after cancer diagnosis	7.5	3.8	9.4	2.8	4.4	3.1	<0.0001

							Chi-squared p-value
Age at diagnosis (years)	63.2	14.2	59.1	13.4	69.8	12.8	<0.0001
	N	%	N	%	N	%	
18- 64 years	229,697	50.7	176,477	76.8	53,220	23.2	
≥ 65 years	223,315	49.3	104,791	46.9	118,524	53.1	
Major depressive disorder (diagnosed at any time during the study period)							<0.0001
Yes	8,999	2.0	3,396	37.7	5,603	62.3	
No	444,013	98.0	277,872	62.6	166,141	37.4	
Number of comorbidities other than depression (diagnosed at any time during the study period)							<0.0001
0-1	116,780	25.8	86,829	74.4	29,951	25.7	
2-3	175,854	38.8	118,747	67.5	57,107	32.5	
≥ 4	160,378	35.4	75,692	47.2	84,686	52.8	
Sex							<0.0001
Female	225,964	49.9	147,033	65.1	78,931	34.9	
Male	227,034	50.1	134,228	59.1	92,806	40.9	

Ethnic concentration quintile							<0.0001
Q1	93,918	21.0	54,131	57.6	39,787	42.4	
Q2	90,603	20.2	53,792	59.4	36,811	40.6	
Q3	87,112	19.5	54,318	62.4	32,794	37.7	
Q4	85,270	19.0	54,954	64.5	30,316	35.6	
Q5	91,025	20.3	61,362	67.4	29,663	32.6	
Neighborhood income quintile							<0.0001
Q1	80,287	17.8	45,465	56.6	34,822	43.4	
Q2	89,497	19.8	53,502	59.8	35,995	40.2	
Q3	89,011	19.7	55,218	62.0	33,793	38.0	
Q4	93,710	20.8	60,303	64.4	33,407	35.7	
Q5	98,694	21.9	65,688	66.6	33,006	33.4	
Rural							<0.0001
No	389,767	86.1	244,246	62.7	145,521	37.3	
Yes	62,725	13.9	36,671	58.5	26,054	41.5	
Cancer type							<0.0001
Breast	77,405	17.1	56,619	73.2	20,786	26.9	
Colon and Rectum	56,897	12.6	30,883	54.3	26,014	45.7	
Digestive System,	21,244	4.7	7,838	36.9	13,406	63.1	

except Colon and Rectum							
Female Genital	30,739	6.8	20,594	67.0	10,145	33.0	
Hematological	39,841	8.8	22,714	57.0	17,127	43.0	
Lung and Bronchus	29,398	6.5	7,634	26.0	21,764	74.0	
Other	84,797	18.7	58,263	68.7	26,534	31.3	
Prostate	83,415	18.4	60,510	72.5	22,905	27.5	
Urinary System	29,276	6.5	16,213	55.4	13,063	44.6	
Cancer stage							<0.0001
I	76,985	17.0	59,775	77.6	17,210	22.4	
II	97,798	21.6	69,856	71.4	27,942	28.6	
III	48,880	10.8	24,946	51.0	23,934	49.0	
IV	30,187	6.7	7,799	25.8	22,388	74.2	
Unknown	199,162	44.0	118,892	59.7	80,270	40.3	

[a]Percentages are column percentages

[b]Percentages are row percentages

As shown in Table 2, MDD is associated with all patient characteristics, especially number of chronic diseases. Only 0.7% had MDD among patients with 0-1 comorbidities whereas 1.5% had MDD among patients with 2-3 comorbidities and 3.5% had MDD among

patients with 4 or more comorbidities. Prevalence of MDD was higher (more than 2.5%) in digestive system except colorectal, hematological, and lung and bronchus cancers.

Table 2

Characteristics of the sample according to MDD[a] (Cancer patients aged ≥ 18 years who survived at least a year following cancer diagnosis)

Variable	No MDD		MDD		
	(N=444,013 (98.0%))		(N=8,999 (2.0%))		
	Mean	*SD*	*Mean*	*SD*	*ANOVA p-value*
Number of years after cancer diagnosis in the study	7.6	3.8	6.5	3.8	<0.0001
	N	*%*	*N*	*%*	*Chi-squared p-value*
Number of comorbidities other than MDD					<0.0001
0-1	116,007	99.3	773	0.7	
2-3	173,177	98.5	2,677	1.5	
≥ 4	154,829	96.5	5,549	3.5	
Age at diagnosis					<0.0001
18- 64 years	225,406	98.1	4,291	1.9	
≥ 65 years	218,607	97.9	4,708	2.1	
Sex[c]					<0.0001
Female	221,007	97.8	4,957	2.2	
Male	222,992	98.2	4,042	1.8	

Ethnic concentration quintile					0.0005
Q1	91,997	98.0	1,921	2.1	
Q2	88,731	97.9	1,872	2.1	
Q3	85,357	98.0	1,755	2.0	
Q4	83,608	98.1	1,662	2.0	
Q5	89,376	98.2	1,649	1.8	
Neighborhood income quintile					<0.0001
Q1	78,051	97.2	2,236	2.8	
Q2	87,561	97.8	1,936	2.2	
Q3	87,355	98.1	1,656	1.9	
Q4	92,146	98.3	1,564	1.7	
Q5	97,127	98.4	1,567	1.6	
Rural					<0.0001
No	382,208	98.1	7,559	1.9	
Yes	61,289	97.7	1,436	2.3	
Cancer type					<0.0001
Breast	75,922	98.1	1,483	1.9	
Colon and Rectum	55,739	98.0	1,158	2.0	
Digestive System, except Colon and Rectum	20,706	97.5	538	2.5	
Female Genital	30,142	98.1	597	1.9	
Hematological	38,824	97.4	1,017	2.6	
Lung and Bronchus	28,538	97.1	860	2.9	
Other	83,169	98.1	1,628	1.9	

Prostate	82,302	98.7	1,113	1.3	
Urinary System	28,671	97.9	605	2.1	
Cancer stage					<0.0001
I	75,600	98.2	1,385	1.8	
II	96,159	98.3	1,639	1.7	
III	47,887	98.0	993	2.0	
IV	29,547	97.9	640	2.1	
Unknown	194,820	97.8	4,342	2.2	

[a]Percentages are row percentages

Survival Analysis: Kaplan-Meier survival curves (Figure 1) indicate that cancer patients with MDD had statistically significant lower (p<0.001) survival probability compared to those without MDD.

Figure 1

Survival probability of cancer patients aged ≥ 18 years by hospital discharge diagnosis of MDD
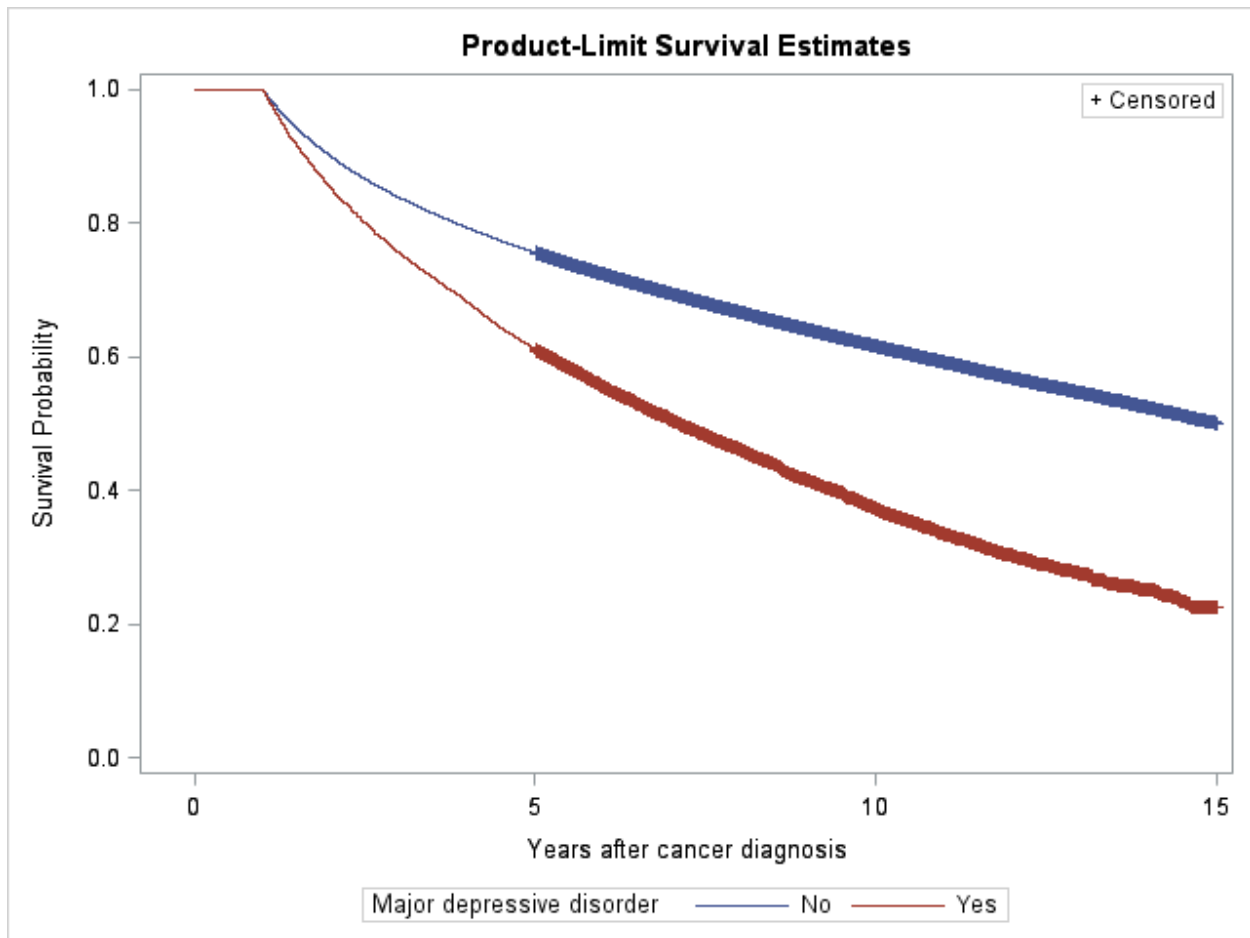
Analyses also showed that survival varied significantly according to number of comorbidities other than MDD (See Appendix C). As shown in Figure 2, survival varied for different combinations of MDD and number of other comorbidities. Among those without MDD, survival probability was highest among those with 0-1 comorbidities and lowest among ≥ 4 comorbidities. However, among those with MDD, in the beginning, survival probability was highest for patients with ≥ 4 comorbidities, and after around 11 years, survival probability was highest for those with 0-1 comorbidities. On further examination, it was found that 26.4% of

patients with depression and 0-1 comorbidities had stage III or stage IV cancers whereas it was

22% for 2-3 comorbidities and 15.1% for 4 or more comorbidities. This might have contributed

to the lower survival probability for patients with 0-1 comorbidities. Also, for those with 2 or

more comorbidities, the other comorbidities might have occurred later during the follow-up

period, hence the greater impact towards the end. Since Kaplan-Meir curves are only

descriptive, adjusted analysis using Cox models will be performed to further explore the effect of

MDD on cancer survival according to number of comorbidities.

Figure 2

Survival probability of cancer patients aged ≥ 18 years by MDD and number of comorbidities
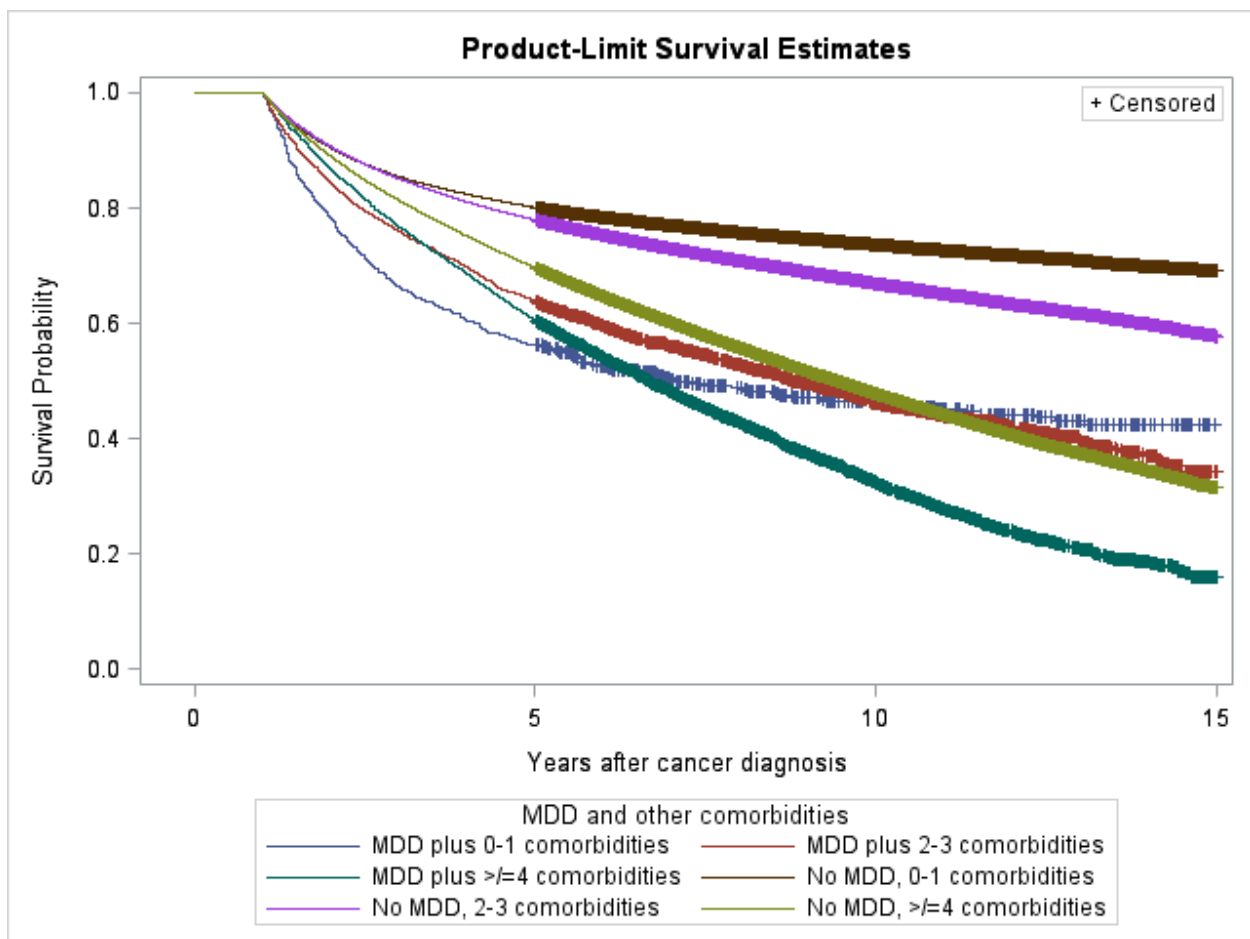
Multivariate Analyses

Adjusted Impact of MDD on Cancer Survival: The Cox model for studying the overall impact of MDD on cancer survival found an adjusted hazard ratio (HR) of 1.58 (95% CI 1.54-1.63) (results not shown), which means that at any point during the study period a cancer patient with MDD was 58% more likely to die than a cancer patient without MDD. Therefore, cancer patients with MDD are likely to die faster than those without MDD. Sensitivity analysis was conducted by doing stratified Cox regression for those who were in the study for less than five years and those who were in the study for five years or more. It showed that depression was not a statistically significant predictor for cancer patients who survived less than five years (results not shown).

The impact of MDD varied according to the number of comorbidities (Table 3). The impact was highest for patients with 0-1 comorbidities (HR 2.55; 95% CI 2.31-2.81) and lowest for patients with ≥ 4 comorbidities other than MDD (HR 1.44; 95% CI 1.40-1.49).

To understand whether the impact of MDD varied according to age at cancer diagnosis, analysis stratified by age group was performed including the interaction variable for MDD and number of comorbidities. Among patients with ≥ 4 comorbidities, impact of MDD was higher in the <65 years group (HR 1.62; 95% CI 1.52-1.73) than the ≥ 65 years group (HR 1.39; 95% CI 1.34-1.45) (See Appendix D). At the other two levels of multimorbidity, the confidence intervals overlapped implying that there was no significant difference in the impact of MDD on survival between the two age groups.

Table 3

Adjusted* impact of MDD on mortality for cancer patients aged ≥ 18 years who survived at least one year following cancer diagnosis

Variable	HR	95% CI
MDD		
0-1 comorbidities (MDD Yes vs No)	2.55	2.31 - 2.81
2-3 comorbidities (MDD Yes vs No)	1.85	1.75 - 1.95
≥ 4 comorbidities (MDD Yes vs No)	1.44	1.40 - 1.49
Age		
18 - 64 years	ref	
≥ 65 years	2.52	2.49 - 2.55
Sex		
Male	ref	
Female	0.79	0.78 - 0.80
Ethnic Concentration Quintile		
Q5	ref	
Q1	1.27	1.25 - 1.29
Q2	1.27	1.25 - 1.29
Q3	1.20	1.19 - 1.22
Q4	1.14	1.12 - 1.16
Neighborhood income quintile		
Q5	ref	
Q1	1.29	1.27 - 1.31
Q2	1.18	1.16 - 1.19
Q3	1.13	1.11 - 1.14
Q4	1.07	1.05 - 1.09
Rural		
No	ref	
Yes	1.01	0.99 - 1.02
Cancer type		

Other	ref	
Breast	1.00	0.98 - 1.02
Colon and Rectum	1.14	1.12 - 1.16
Digestive System, except Colon and Rectum	2.30	2.26 - 2.35
Female Genital	1.39	1.36 - 1.42
Hematological	1.14	1.12 - 1.16
Lung and Bronchus	2.74	2.69 - 2.80
Prostate	0.55	0.54 - 0.56
Urinary System	1.08	1.05 - 1.10
Cancer Stage		
I	ref	
II	1.64	1.60 - 1.67
III	2.77	2.72 - 2.83
IV	5.89	5.77 - 6.01
Unknown	1.91	1.88 - 1.94

*Result of Cox proportional hazards regression with the interaction term between MDD and

number of comorbidities and confounding variables included in the model

Adjusted Impact of MDD on Cancer Survival Stratified by Cancer Type: Analysis stratified by cancer type showed that there were differences in the impact of MDD on survival between different types of cancer, although the differences were not statistically significant between all cancer types (See Table 4). The impact was highest for prostate cancer patients (HR 1.92; 95% CI 1.77-2.08) and lowest for lung and bronchus cancer patients (HR 1.20; 95% CI 1.11-1.30). Interaction between MDD and number of comorbidities showed that the impact of MDD did not vary significantly according to number of comorbidities in breast, female genital, and lung and bronchus cancers.

Table 4

Adjusted impact of MDD on mortality according to type of cancer for patients aged ≥ 18 years who survived at least one year following cancer diagnosis, overall (without interaction), and by number of comorbidities other than MDD (with interaction between MDD and number of comorbidities)

Cancer type	HR	95% CI
Breast[a]	1.72	1.59 - 1.85
Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	2.00	1.50 - 2.67
2-3 comorbidities (MDD Yes vs No)	1.97	1.70 - 2.28
≥ 4 comorbidities (MDD Yes vs No)	1.62	1.48 - 1.77
Colon and Rectum[a]	1.65	1.53 - 1.77
Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	2.58	2.00 - 3.33
2-3 comorbidities (MDD Yes vs No)	1.78	1.55 - 2.05
≥ 4 comorbidities (MDD Yes vs No)	1.54	1.41 - 1.68

Digestive System, except Colon and Rectum[ab]	1.23	1.11 - 1.36
Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	1.90	1.42 - 2.56
2-3 comorbidities (MDD Yes vs No)	1.37	1.15 - 1.64
≥ 4 comorbidities (MDD Yes vs No)	1.08	0.94 - 1.24
Female Genital[a]	1.63	1.46 - 1.82
Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	2.05	1.50 - 2.79
2-3 comorbidities (MDD Yes vs No)	1.91	1.58 - 2.31
≥ 4 comorbidities (MDD Yes vs No)	1.42	1.21 - 1.65
Hematological[a]	1.55	1.43 - 1.68
Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	3.03	2.26 - 4.07
2-3 comorbidities (MDD Yes vs No)	1.87	1.60 - 2.17
≥ 4 comorbidities (MDD Yes vs No)	1.38	1.25 - 1.52
Lung and Bronchus[a]	1.20	1.11 - 1.30
Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	1.72	1.28 - 2.31
2-3 comorbidities (MDD Yes vs No)	1.19	1.03 - 1.39
≥ 4 comorbidities (MDD Yes vs No)	1.17	1.07 - 1.28
Other[a]	1.75	1.64 - 1.87
Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	3.37	2.70 - 4.21
2-3 comorbidities (MDD Yes vs No)	1.88	1.64 - 2.15
≥ 4 comorbidities (MDD Yes vs No)	1.60	1.48 - 1.74
Prostate	1.92	1.77 - 2.08

Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	3.76	2.45 - 5.78
2-3 comorbidities (MDD Yes vs No)	2.93	2.48 - 3.47
$\geq$ 4 comorbidities (MDD Yes vs No)	1.71	1.56 - 1.87
Urinary System[a]	1.56	1.41 - 1.73
Impact of MDD by number of comorbidities other than depression[*]		
0-1 comorbidities (MDD Yes vs No)	1.61	0.98 - 2.64
2-3 comorbidities (MDD Yes vs No)	1.95	1.53 - 2.49
$\geq$ 4 comorbidities (MDD Yes vs No)	1.49	1.33 - 1.67

[*]Result of Cox proportional hazards regression stratified by cancer type with the interaction term between MDD and number of comorbidities and confounding variables (age group, sex, ethnic concentration quintile, neighborhood income quintile, rurality of residence, cancer stage) included in the model

[a]Rural not significant

[b]Number of comorbidities not significant

Discussion

This study examined whether MDD had an impact on the survival of cancer patients with or without other comorbidities. The results showed that cancer patients with MDD had a poorer survival than those without MDD. However, the impact of MDD on survival was not significant for patients who were in the study for less than five years. The overall adjusted impact of depression on survival was higher in patients aged < 65 years when compared to those aged $\geq$ 65 years.

The study results are consistent with the results of past non-Canadian studies that have shown that depression has a negative impact on the survival of cancer patients (Chang et al., 2014; Kanani et al., 2016; Low et al., 2016; Sun et al., 2015; Warnke et al., 2016). The studies by Chang et al. (2014) and Sun et al. (2015) were also population-based and included all types of cancer. However, they found lower estimates of the impact of depression than this study, most likely because they would have included milder cases of depression. Chang et al. (2014) identified depression from all psychiatric diagnoses and estimated a 30% higher mortality risk (HR 1.30; 95% CI 1.11-1.54) in depressed patients. Sun et al. (2014) identified depression from antidepressant use and found that current use was associated with 32% (mortality rate ratio 1.32; 95% CI 1.29–1.35) higher one-year mortality overall and 22% (mortality rate ratio 1.22; 95% CI 1.17–1.26) higher five-year mortality among those who survived the first year after cancer diagnosis (Sun et al., 2015). Various meta-analyses examining the impact of depression on cancer survival have also shown that depression is associated with a higher risk of death (Pinquart & Duberstein, 2010; Satin et al., 2009; Wang et al., 2019).

The meta-analysis by Pinquart & Duberstein found that studies with shorter follow-up period (2 years or less) and in older patients showed stronger association between depression and cancer survival (Pinquart & Duberstein, 2010). This is in contrast with our study since our results showed no association between depression and cancer survival in those who survived less than five years (although we excluded patients who survived less than a year after cancer diagnosis) and lesser impact of depression on the survival of cancer patients in the older compared to the younger age group. In Ontario all residents become eligible for prescription drug coverage through ODB when they turn 65 years of age, increasing the likelihood of filling antidepressant prescriptions by that age group. Hence their depression may be better controlled resulting in the

reduced impact of depression on their survival. Similar to our study, Prieto et al. (2005) also found no significant association between depression and five-year survival although their sample included only hematological cancer patients with stem-cell transplantation.

Prevalence of multimorbidity was high in the sample, with 74% patients having 2 or more comorbidities other than MDD. Number of comorbidities had a modifying effect on the impact of MDD on cancer survival. Patients with 0-1 comorbidities showed the highest impact of MDD on survival and patients with ≥ 4 comorbidities showed the lowest impact. The reason might be that the severity of other comorbidities had a greater impact on survival than MDD in patients with more comorbidities. Since we did not include the severity of comorbidities in our analyses it is not possible to ascertain whether that is the reason for the decreased impact of depression on survival when the number of other comorbidities increased. Another reason might be the frequent health system encounters due to higher number of comorbidities leading to earlier diagnosis (Akincigil & Matthews, 2017) and better management of MDD.

There was a higher prevalence of MDD in cancers of poorer prognosis, although the impact of MDD on survival in such cancer types was lower. Because of clinical differences, cancer types might influence the impact of MDD on survival. Stratified analysis showed that in breast, colorectal, female genital, prostate, and 'other' cancers, patients with MDD had more than 60% higher mortality than those without MDD. Routine screening can lead to earlier diagnosis of breast, prostate, colorectal and cervical cancers resulting in a better prognosis. The reason why the impact of depression on survival is higher in those patients may be that because they are likely to live longer, there is a longer timespan in which depression can influence the patients' health-related behaviors, such as adherence to treatment and maintaining a healthy lifestyle, which in turn can affect their longevity. Other studies have also shown that depression

is associated with higher mortality among those cancer types (Liang et al., 2017; P.-H. Lin et al., 2018; Lu et al., 2019; Suppli et al., 2017; Vodermaier et al., 2014). Similar to our findings, population-based studies in British Columbia, Canada, have also reported that depression was associated with poorer survival among lung (Vodermaier et al., 2017) and breast cancer patients (Vodermaier et al., 2014). Lowest impact of MDD on survival was found in digestive system except colorectal and in lung and bronchus cancers, although patients with those types of cancers had a higher prevalence of MDD. Those cancer types also had the highest percentage of deceased patients. The greater severity and overall poorer prognosis for those cancer types might have impacted the mental health of the patients and contributed to increased risk of MDD, without MDD being the main reason of death. It can be inferred that the lower survival time for those patients limited the duration of effect of MDD and hence the lower impact of MDD on survival.

Overall, in all types of cancer, the highest impact of MDD on survival was in patients with 0-1 comorbidities and lowest impact in patients with $\geq$ 4 comorbidities, although the differences in impact according to multimorbidity was not significant for breast, female genital, and lung and bronchus cancers. A study in the USA investigating the impact of pre-existing mental health disorders on lung cancer survival showed that the impact was statistically significant in patients with no comorbidities (HR 1.15, 95% CI 1.01-1.31) and one comorbidity (HR 1.18, 95% CI 1.01-1.39) and not significant in those with 2 or more comorbidities (HR 1.07, 95% CI 0.95-1.20) (J. Lin et al., 2016). Our study showed a significant impact of MDD on the survival of lung and bronchus cancer patients at all the three levels of multimorbidity, although difference between the impacts of MDD at different levels of multimorbidity was not statistically significant. Our study differed from the study by J. Lin et al. (2016) in that their sample was

from the military health system who typically have a high prevalence of mental health disorders and substance abuse (Hoge et al., 2004). Their exposure was any pre-existing mental health disorder, including post-traumatic stress disorder and psychotic disorder, whereas our exposure was MDD diagnosed both before and after cancer diagnosis. Their analyses were adjusted for confounders such as smoking, marital status, tumor grade and histology, types of treatment, and recurrence status.

Overall, this study showed that MDD was a key predictor of cancer survival. More generally, however, mental health needs of cancer patients can be complex as evidenced by 40% of the whole sample and 80.7% of patients with MDD having a mental health disorder besides MDD (See Appendix B). Hence, mental health care is important in the management of cancer patients.

Limitations

This study may be subject to misclassification bias due to methods used for identifying depression and other health conditions and accuracy of coding in the administrative data. If the patient or the physician does not give importance to mental health symptoms, depression may not be recognized. We could only include the diagnosis of MDD in hospitalized patients (identified using ICD 10 codes) for this study since the ICD 9 codes recorded for outpatient visits did not have more than three digits, preventing the identification of MDD separate from other episodic mood disorders. This has resulted in underestimating the depression prevalence. In hospitalized patients, a mental health diagnosis is likely to be specified only if it is very apparent and not well-controlled, which could also lead to underestimation of depression. In other words, we recognize that our analysis likely reflects the impact of severe depression, as mild and moderate depression is unlikely to be diagnosed in hospital. The annual prevalence of major

depression in Canada is around 5% (Patten et al., 2016), which is significantly higher than our estimate.

Since many patients included in the non-exposed group (no MDD) might have had outpatient diagnosis of MDD, the resulting misclassification bias might have attenuated the study estimates (type II error). If all patients with MDD (diagnosed in hospital as well as outpatient settings) had been included in the exposed group, the HR estimates would likely be higher, although there is a chance that less severe MDD diagnosed in outpatient settings may not have as high an impact on survival as MDD diagnosed during hospitalizations. Another problem associated with identifying MDD only in hospitalized patients is that generally cancer patients are hospitalized when they have severe symptoms and there is a high rate of in-hospital deaths in cancer patients who are hospitalized (Numico et al. 2015). Hence, the patients identified as having MDD in this study might have been already in a critical condition to warrant hospitalization. So, there is a possibility of reverse causality in this study. There is also the possibility of differential misclassification since patients who are more likely to have the outcome (death) are also more likely to be diagnosed with MDD during a hospitalization (exposure).

There are other chronic diseases, such as genetic disorders and congenital malformations, which were not included and hence the number of comorbidities in our study population might be an underestimation. The study did not consider the severity of comorbidities for estimating the level of multimorbidity. A patient with one severe chronic disease may have shorter survival than a patient with three chronic diseases that are well-controlled. Information regarding confounders such as marital status, diet, physical activity, smoking, and alcohol use were not available and hence we were unable to adjust the analyses for those confounders. Other potential

confounders which were not included are health care related factors such as access to care and quality of care.

Strengths

The large sample size of our study minimizes selection bias and facilitates decision-making better than studies on smaller samples. The longer follow-up period (7.5 years in average) is another strength of this study, which allowed the assessment of longer-term survival among cancer patients. The results of stratified analyses may help in developing specially tailored programs for improving the survival of cancer patients according to multimorbidity and cancer type.

Conclusions

This study showed that depression has a negative impact on the survival of cancer patients in Ontario and that the impact varies according to the number of other comorbidities present in a patient. The results stress the importance of identifying and properly addressing depression in cancer patients, especially in the context of multimorbidity. The finding that MDD impacts survival in all cancer types, even if the impact in cancers with poorer survival is smaller, emphasizes that depression should be diagnosed and treated in patients with all types of cancer. Proper diagnosis and treatment of cancer patients with MDD may improve their adherence to treatment and lifestyle recommendations and quality of life, leading to longer survival. Future studies should investigate the combined impact of all mental health disorders on cancer and multimorbidity survival as mental health disorders of all kinds and their treatment are likely to affect outcomes of cancer patients.

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Appendix A

ICES databases used for obtaining data for the study

Database	Description	Variables
Discharge Abstract Database (DAD)	Information on hospitalizations in Ontario. Includes admissions, length of stay and discharges.	Major depressive disorder using the diagnosis codes, time of diagnosis
Ontario Cancer Registry (OCR)	Information on all Ontario residents diagnosed with cancer. Includes date of diagnosis, site of primary cancer and cancer deaths.	Age at diagnosis, sex, primary cancer site, stage at diagnosis, time of death
Ontario Health Insurance Plan (OHIP) claims database	Information on claims paid for by OHIP. Includes physician visits, hospitalizations and associated diagnosis.	Comorbidities including depression using the diagnostic codes, time of diagnosis
Registered Persons Database (RPDB)	Demographic information for all individuals who have ever had a valid Ontario health card number. Includes age, sex, neighbourhood income and residence.	Neighbourhood income quintile, rurality, time of death
National Ambulatory Care Reporting System (NACRS)	Information on outpatient visits to hospital and community-based ambulatory care. Includes day surgery, outpatient clinics, and emergency departments.	Comorbidities including depression using the diagnostic codes, time of diagnosis
Ontario Marginalization Index (ON-Marg)	Information regarding deprivation or marginalization based on residential instability, material	Ethnic concentration quintile

	deprivation, dependency, and
	ethnic concentration

Appendix B

ICD codes and prevalence of chronic conditions

Condition	ICD 9 / OHIP	ICD 10	Prevalence (%)
Acute myocardial infarction	410	I21, I22	4.41
Arthritis - Osteoarthritis	715	M15-M19	50.48
Arthritis - Rheumatoid arthritis	714	M05-M06	3.25
Asthma	493	J45	14.19
Cancer	140-239	C00-C26, C30-C44, C45-C97,	
Cardiac Arrythmia	427.3 (DAD) / 427 (OHIP)	I48.0, I48.1	13.43
Congestive heart failure	428	I500, I501, I509	13.86
COPD	491, 492, 496	J41, J43, J44	13.69
Dementia	290, 331, 797 (OHIP) / 290.0, 290.1, 290.3, 290.4, 290.8, 290.9, 294.1, 294.8, 294.9, 331.0, 331.1, 331.2, 797 (DAD)	F000, F001, F002, F009, F010, F011, F012, F013, F018, F019, F020, F021, F022, F023, F024, F028, F03, F051, F065, F066, F068, F069,	6.97

		F09, G300, G301, G308, G309, G310, G311, R54	
Major depressive disorder		F32, F33	1.99
Diabetes	250	E08 - E13	28.57
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15	62.99
Osteoporosis	733	M81 M82	7.64
Renal failure	403,404,584,585,586,v451	N17, N18, N19, T82.4, Z49.2, Z99.2	12.63
Stroke	430, 431, 432, 434, 436	I60-I64	6.36
Coronary syndrome (excluding MI)	411-414	I20, I22-I25	21.25
Other mental disorders (substance use disorder, psychotic disorder, mood disorder-with specific flag for MDD, anxiety, stress reaction-specifically PTSD, personality disorder)	291, 292, 303, 304, 305, 295, 298, 297, 296, 300, 308, 301	F10-F19, F55, F20-F29, F30-F34, F38, F39, F40-F42, F93, F43, F60	39.88

Appendix C

Survival probability of cancer patients aged ≥ 18 years by number of comorbidities
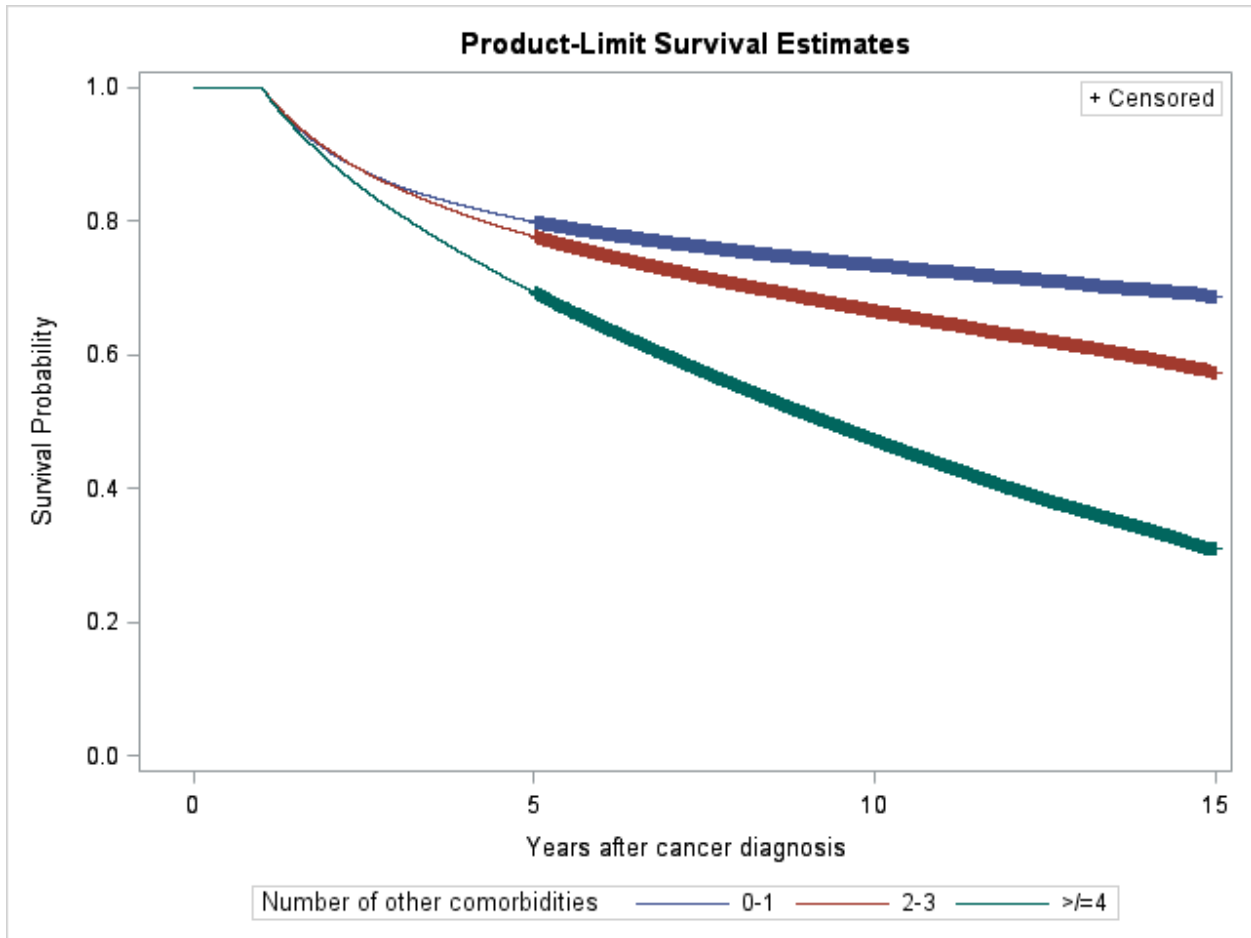
Appendix D

Adjusted impact[*] of MDD on mortality for cancer patients aged ≥ 18 years who survived at least one year following cancer diagnosis, stratified by age group with interaction of MDD and number of comorbidities

	< 65 years		≥ 65 years	
Variable	HR	95% CI	HR	95% CI
MDD				
0-1 comorbidities (MDD Yes vs No)	2.46	2.19 - 2.77	2.57	2.13 - 3.10
2-3 comorbidities (MDD Yes vs No)	1.84	1.71 - 1.98	1.77	1.64 - 1.91
≥ 4 comorbidities (MDD Yes vs No)	1.62	1.52 - 1.73	1.39	1.34 - 1.45
Sex				
Male	ref			
Female	0.72	0.70 - 0.73	0.84	0.83 - 0.85
Ethnic Concentration Quintile				
Q5	ref			
Q1	1.30	1.26 - 1.34	1.23	1.21 - 1.26
Q2	1.27	1.24 - 1.31	1.25	1.23 - 1.28
Q3	1.19	1.16 - 1.23	1.20	1.18 - 1.22
Q4	1.13	1.10 - 1.16	1.14	1.12 - 1.16
Neighborhood income quintile				
Q5	ref			
Q1	1.32	1.29 - 1.36	1.27	1.24 - 1.29

Q2	1.23	1.20 - 1.27	1.15	1.13 - 1.17
Q3	1.17	1.14 - 1.20	1.11	1.09 - 1.13
Q4	1.10	1.07 - 1.13	1.06	1.04 - 1.08
Rural				
No	ref			
Yes	1.04	1.01 - 1.07	1.00	0.98 - 1.01
Cancer type				
Other	ref			
Breast	1.31	1.26 - 1.35	0.82	0.80 - 0.84
Colon and Rectum	1.56	1.51 - 1.61	0.93	0.91 - 0.95
Digestive System, except Colon and Rectum	3.40	3.28 - 3.52	1.78	1.73 - 1.82
Female Genital	1.92	1.85 - 2.00	1.13	1.09 - 1.16
Hematological	1.21	1.17 - 1.25	1.05	1.03 - 1.08
Lung and Bronchus	4.60	4.46 - 4.75	2.11	2.06 - 2.16
Prostate	0.48	0.46 - 0.50	0.52	0.51 - 0.53
Urinary System	1.25	1.20 - 1.30	0.94	0.92 - 0.97
Cancer Stage				
I	ref			
II	2.14	2.06 - 2.22	1.44	1.41 - 1.47
III	4.27	4.11 - 4.42	2.22	2.16 - 2.27
IV	9.89	9.53 - 10.26	4.35	4.24 - 4.47
Unknown	2.33	2.25 - 2.41	1.72	1.69 - 1.76

*Result of Cox proportional hazards regression with the interaction term between MDD and

number of comorbidities and confounding variables included in the model

Chapter 5: Impact of Adequate Antidepressant Refill on the Survival of Older Cancer

Patients with Depression

Abstract

Aim: To evaluate the impact of adequate antidepressant refill (AAR – defined as 180 days' continuous refill of antidepressants) on the survival of older cancer patients with major depressive disorder (MDD).

Methods: A population-based retrospective cohort study was conducted on all cancer patients aged ≥ 65 years in Ontario, Canada, who were diagnosed with cancer between April 2003 and March 2013, survived at least a year following cancer diagnosis, and had a hospital discharge diagnosis of MDD before or during the study period. They were followed until March 2018. Cox proportional hazards regression was performed adjusting for covariates.

Results: Among the sample (N=4,708; 51.5% females; median age at cancer diagnosis 75 years), 67.7% were diagnosed with MDD after cancer. 76.9% died during the study and 65.5% received AAR. Overall, AAR was associated with lower risk of mortality (adjusted hazard ratio (aHR) 0.58; 95% confidence interval (CI) 0.54-0.62). Further testing showed that the impact of AAR on mortality was statistically significant only for patients whose MDD was diagnosed after cancer (aHR 0.51; 95% CI 0.47-0.55). Analysis stratified by cancer type showed that the impact of AAR on mortality did not vary significantly between all cancer types. In patients whose MDD was diagnosed before cancer, AAR had a statistically significant impact only in lung and bronchus cancers and digestive system cancers except colorectal. Among patients whose MDD was diagnosed after cancer, AAR was associated with lower mortality in all cancer types.

Conclusion: AAR is associated with better survival among cancer patients with MDD if MDD is diagnosed after cancer.

Impact of Adequate Antidepressant Refill on the Survival of Older Cancer Patients with

Depression

Depression is a mood disorder which affects cancer patients more than the rest of the population (Watts et al., 2015). Depending on the severity of cancer, prevalence of depression among cancer patients ranges from 5% to 50% (Walker et al., 2013). Depression is associated with lesser likelihood for undergoing cancer screening (Silberbogen et al., 2014) and receiving definitive treatments for cancer (Prasad et al., 2014). They are also likely to have poor adherence to treatment recommendations (Moraes & Casseb, 2017). Depressed patients are at a high risk of having unhealthy behaviours such as poor diet, alcoholism, (Barros et al., 2017), smoking, drug use (Ruggles et al., 2017), and physical inactivity (Chipperfield et al., 2013), which can impact their survival. Studies have shown that depression can negatively impact the survival of cancer patients (Chang et al., 2014; Shinn et al., 2016).

Depression in cancer patients can be managed by using antidepressants or employing psychological or psychosocial interventions (Li et al., 2016) and treatment of depression can improve the quality of life among cancer patients (Nikbakhsh et al., 2018). Antidepressant therapy is considered as a first-line treatment for severe depression in cancer patients (Li et al., 2016). It is recommended that a patient should take an antidepressant dose for around one to two months to attain its full benefits (American Psychiatric Association, 2010) and continue using the antidepressant for at least six months following symptom remission (National Health Service, 2018).

More than 50% of new cancer diagnoses occur in those who are 65 years of age or older (National Cancer Institute, 2015). Among older cancer patients, the prevalence of clinical depression ranges from 3% to 25% according to a review of literature (Kua, 2005). Non-

pharmacological methods for managing depression including problem-solving therapy and cognitive behavioral therapy have been found to be beneficial in older patients with depression (Jonsson et al., 2016). First-line antidepressants recommended in older patients such as selective serotonin reuptake inhibitors (SSRIs) and selective serotonin noradrenaline reuptake inhibitors (SSNRIs) have been found to have similar risk of mortality as citalopram, which is a commonly prescribed SSRI (Kollhorst et al., 2019).

There are some risks associated with antidepressant use in cancer patients. SSRI use has been found to be associated with higher mortality among breast cancer patients (Busby et al., 2018) and with faster disease progression among ovarian cancer patients (Christensen et al., 2016). Studies among lung cancer patients have shown conflicting results about the impact of antidepressant use on survival (Sullivan et al., 2014; Zingone et al., 2017). Hence, antidepressants are prescribed to cancer patients only when the benefits outweigh the risks (Li et al., 2016).

Although there are studies on the impacts of different types of depression treatment in older patients (Jonsson et al., 2016; Kollhorst et al., 2019) and in cancer patients (Okuyama et al., 2017; Ostuzzi et al., 2018), there is a paucity of research examining the impact of antidepressant use in older cancer patients with depression (Ostuzzi et al., 2018). This study aims to estimate the impact of adequate antidepressant refill (AAR) on the survival of older cancer patients with depression, specifically major depressive disorder (MDD).

Methods

Study Design and Data Sources

The population-based health administrative data available from the Institute for Clinical Evaluative Sciences (ICES) were used to conduct retrospective cohort study in Ontario, Canada.

ICES, which is a non-profit research organization (Institute for Clinical Evaluative Sciences, n.d.a), collects health care data of Ontario residents from various sources such as physician and hospital records (Institute for Clinical Evaluative Sciences, n.d.b). Different databases maintained at ICES were linked using the patients' unique ICES codes to obtain information about inpatient services, outpatient services, and drugs (Institute for Clinical Evaluative Sciences, n.d.b). The databases used include Ontario Cancer Registry, Ontario Marginalization Index, Registered Persons Database, Ontario Health Insurance Plan claims database, Discharge Abstract Database, Ontario Drug Benefit claims database and National Ambulatory Care Reporting System. See Appendix A for details about the databases used for the study. Ethics approval was obtained from ICES and Lakehead University Research Ethics Board.

Study Population

All cancer patients in Ontario diagnosed between April 1, 2003 and March 31, 2013 who were at least 65 years old and had a hospital discharge diagnosis of MDD were included in the study. All Ontario residents become eligible for provincial drug coverage under the Ontario Drug Benefit (ODB) program when they become 65 years old (Ontario, 2019) and information about drug refills is available from the ODB database for that age group. The cohort was followed until March 31, 2018 to measure survival. MDD was identified using the ICD 10 codes F32 (Major depressive disorder, single episode) and F33 (Major depressive disorder, recurrent) from the Discharge Abstract Database on hospitalized patients at any point during the study period or up to three years before the beginning of the study. Patients who were more than 105 years old and those with invalid health card numbers were excluded. Patients who died within one year of cancer diagnosis were also excluded from the study to minimize reverse causality.

There were 334,740 cancer patients, 65 years or older, who were diagnosed with cancer between April 1, 2003 and March 31, 2013. Among them, 7,254 (2.17%) had a hospital discharge diagnosis of MDD. The study sample was obtained after excluding 2,546 patients (35.1% of patients with MDD) who died within one year of cancer diagnosis. Average age at cancer diagnosis was 77.9 years for the patients who died within a year of cancer diagnosis and 18.5% had stage IV cancer. Stage was unknown for 64.7% of those patients.

Study Measures

The primary outcome, survival time, was available from the Registered Persons Database. Survival time represents number of days from cancer diagnosis to death or until March 31, 2018, for those still alive at the end of the study.

The main exposure, adequate antidepressant refill (AAR), was defined as 180 days of continuous antidepressant refill with no more than 7 days' gap. Adequate antidepressant use was defined as taking antidepressant for 180 days or more, since six months is the recommended minimum duration of antidepressant therapy (Duhoux et al., 2012; National Health Service, 2018). Antidepressants included in this study and their drug identification numbers (DINs) are listed in Appendix B. ODB database has information such as name of medication, DIN, time of fill, and number of days' supply refilled each time, which were used to identify AAR.

Time of MDD (before/after cancer diagnosis) was included as a potential effect modifier of the impact of AAR on survival. Sociodemographic factors such as age at cancer diagnosis, sex, ethnic concentration quintile, neighbourhood income quintile, and rurality of residence and clinical factors such as type of cancer, cancer stage, and number of comorbidities other than MDD were included as confounders. Higher values in the ethnic concentration quintile represent higher concentration of recent immigrants (arrived in Canada in the past 5 years) and visible

minorities (Matheson et al., 2018). Rurality Index of Ontario scores of 0 to 39 were considered as urban and scores 40 and above were considered rural (Glazier et al., 2012). The following chronic diseases were counted for estimating the number of comorbidities other than MDD based on previous research on multimorbidity: osteoarthritis, hypertension, asthma, diabetes, chronic coronary syndrome, cardiac arrhythmia, osteoporosis, chronic obstructive pulmonary disease, congestive heart failure, renal failure, dementia, rheumatoid arthritis, stroke, acute myocardial infarction, and other mental disorders (substance use, psychotic illness, anxiety, other mood disorders, stress, or personality disorder). previous research on multimorbidity (Pefoyo et al., 2015).

Analyses

All analyses were performed using the statistical analysis software SAS (SAS Institute, 2013). Chi-square test and ANOVA were used to assess the bivariate associations between patients' sociodemographic characteristics (age, sex, ethnicity, income, rurality (rural/not rural)), cancer characteristics (type of cancer and stage), number of comorbidities, time of MDD diagnosis, and AAR and vital status. Kaplan-Meier estimates and curves were obtained and log-rank tests performed for bivariate analysis with survival time.

Multivariate analysis was performed using Cox proportional hazards regression to study the adjusted impact of AAR on the risk of death. Interaction of AAR and time of diagnosis of MDD was tested for to examine whether the impact of AAR on survival varied according to time of MDD diagnosis. Since survival varies according to clinical characteristics, stratified analysis for specific types of cancer was conducted to estimate the impact of AAR on the survival of specific cancer types after testing for the effect of interaction between AAR and cancer type.

Results

Descriptive and Bivariate Analyses

The sample included 4,708 cancer patients aged ≥ 65 years with a hospital discharge

diagnosis of MDD. Table 1 shows the characteristics of the whole sample and according to the

outcome, death. On average, patients were in the study for 5.8 years. MDD was diagnosed after

cancer diagnosis in 67.7% of the sample, and 65.5% of the sample received AAR. Overall, 77%

died during the study period. Among those who received AAR, 71% died within the study

period. Among those who did not receive AAR, 88% died during the study.

Table 1

Characteristics of cancer patients with MDD aged ≥ 65 who survived at least a year following

cancer diagnosis, whole sample and according to vital status

Variable	Whole sample (N=4,708)		Alive (N=1,089, 23.1%)		Deceased (N=3,619, 76.9%)		p-value
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*ANOVA p-value*
Number of years in the study	5.8	3.6	9.3	2.8	4.8	3.1	<0.0001
Age at cancer diagnosis (years)	75.5	6.9	72.9	6.0	76.3	6.9	<0.0001
	N	*%*	*N*	*%*	*N*	*%*	*Chi-squared p-value*
AAR							<0.0001
No	1,624	34.5	193	11.9	1,431	88.1	
Yes	3,084	65.5	896	29.1	2,188	71.0	
Time of MDD diagnosis							<0.0001

Before cancer diagnosis	1,525	32.4	436	28.6	1,089	71.4	
After cancer diagnosis	3,183	67.6	653	20.5	2,530	79.5	
Sex							0.0015
Female	2426	51.5	607	25.0	1,819	75.0	
Male	2,282	48.5	482	21.1	1,800	78.9	
Ethnic concentration quintile							0.7872
Q1	1,079	23.3	260	24.1	819	75.9	
Q2	1,017	21.9	225	22.1	792	77.9	
Q3	897	19.3	201	22.4	696	77.6	
Q4	846	18.2	201	23.8	645	76.2	
Q5	802	17.3	190	23.7	612	76.3	
Neighborhood income quintile							0.2292
Q1	1,129	24.1	257	22.8	872	77.2	
Q2	987	21.0	246	24.9	741	75.1	
Q3	856	18.2	181	21.1	675	78.9	
Q4	846	18.0	186	22.0	660	78.0	
Q5	874	18.6	216	24.7	658	75.3	
Rural							0.8698
No	3,945	83.9	914	23.2	3,031	76.8	
Yes	760	16.2	174	22.9	586	77.1	
Cancer type							<0.0001
Breast	696	14.8	218	31.3	478	68.7	

Colon and Rectum	761	16.2	171	22.5	590	77.5	
Digestive System, except Colon and Rectum	240	5.1	32	13.3	208	86.7	
Female Genital	235	5.0	63	26.8	172	73.2	
Hematological	477	10.1	92	19.3	385	80.7	
Lung and Bronchus	505	10.7	66	13.1	439	86.9	
Other	660	14.0	143	21.7	517	78.3	
Prostate	771	16.4	231	30.0	540	70.0	
Urinary System	363	7.7	73	20.1	290	79.9	
Cancer stage							<0.0001
I	649	13.8	217	33.4	432	66.6	
II	909	19.3	268	29.5	641	70.5	
III	474	10.1	89	18.8	385	81.2	
IV	270	5.7	35	13.0	235	87.0	
Unknown	2,406	51.1	480	20.0	1,926	80.0	
Number of comorbidities other than depression							0.0003
< 4	1,069	22.7	291	27.2	778	72.8	
≥ 4	3,639	77.3	798	21.9	2,841	78.1	

While 82.5% of cancer patients whose MDD was diagnosed before cancer diagnosis received AAR, only 57.4% of patients whose MDD was diagnosed after cancer received AAR. There was no significant difference between patients who received AAR and those who did not receive AAR in terms of age and socioeconomic factors such as ethnic concentration quintile, neighborhood income quintile, and rurality of residence (Table 2). Nonetheless, we still included those variables in the analyses because those characteristics can impact cancer survival.

There was a significant difference between those who received AAR and those who did not receive AAR in cancer characteristics such as type of cancer at the time of diagnosis and stage at the time of diagnosis. Percentage receiving AAR varied from 54.6% in patients with digestive system cancer (except colorectal) to 74.4% in patients with breast cancer. Lesser proportion of patients diagnosed with late-stage cancers received AAR compared to patients diagnosed with early-stage cancers (Table 2).

Table 2

Characteristics of cancer patients with MDD aged 65 or above who survived at least a year following cancer diagnosis, according to adequate antidepressant refill

Variable	No AAR (N=1,624; 34.5%)		AAR (N=3,084; 65.5%)		
	Mean	*SD*	*Mean*	*SD*	*ANOVA p-value*
Number of years in the study	4.8	3.3	6.3	3.6	<0.0001
Age (years)	75.4	6.8	75.6	7.0	0.3392
	N	*%*	*N*	*%*	*Chi-squared p-value*

Time of MDD diagnosis					<0.0001
Before cancer diagnosis	267	17.5	1,258	82.5	
After cancer diagnosis	1,357	42.6	1,826	57.4	
Sex					<.0001
Female	751	31.0	1,675	69.0	
Male	873	38.3	1,409	61.7	
Ethnic concentration quintile					0.5153
Q1	368	34.1	711	65.9	
Q2	342	33.6	675	66.4	
Q3	311	34.7	586	65.3	
Q4	287	33.9	559	66.1	
Q5	299	37.3	503	62.7	
Neighborhood income quintile					0.3095
Q1	370	32.8	759	67.2	
Q2	328	33.2	659	66.8	
Q3	304	35.5	552	64.5	
Q4	296	35.0	550	65.0	
Q5	322	36.8	552	63.2	
Rural					0.4879
No	1,370	34.7	2,575	65.3	
Yes	254	33.4	506	66.6	
Cancer type					<0.0001
Breast	178	25.6	518	74.4	
Colon and Rectum	273	35.9	488	64.1	

|					
Digestive System, except Colon and Rectum	109	45.4	131	54.6	
Female Genital	85	36.2	150	63.8	
Hematological	176	36.9	301	63.1	
Lung and Bronchus	185	36.6	320	63.4	
Other	229	34.7	431	65.3	
Prostate	268	34.8	503	65.2	
Urinary System	121	33.3	242	66.7	
Cancer stage					<0.0001
I	179	27.6	470	72.4	
II	295	32.5	614	67.5	
III	190	40.1	284	59.9	
IV	141	52.2	129	47.8	
Unknown	819	34.0	1,587	66.0	
Number of comorbidities other than MDD					<0.0001
< 4	502	47.0	567	53.0	
≥ 4	1,122	30.8	2,517	69.2	

Survival analysis: Kaplan-Meier curves (Figure 1) suggest that cancer patients with MDD had a higher survival probability if they received AAR (<0.001). Patients who were diagnosed with MDD after cancer and did not receive AAR had the lowest survival probability. They had worse survival than patients who were diagnosed with MDD before cancer irrespective of whether patients who were diagnosed with MDD before cancer received AAR or not. Patients

who were diagnosed with MDD after cancer and received AAR had the highest probability of survival.

Figure 1

Survival probability of cancer patients aged ≥ 65 years with MDD who survived at least a year following cancer diagnosis by AAR and time of MDD diagnosis
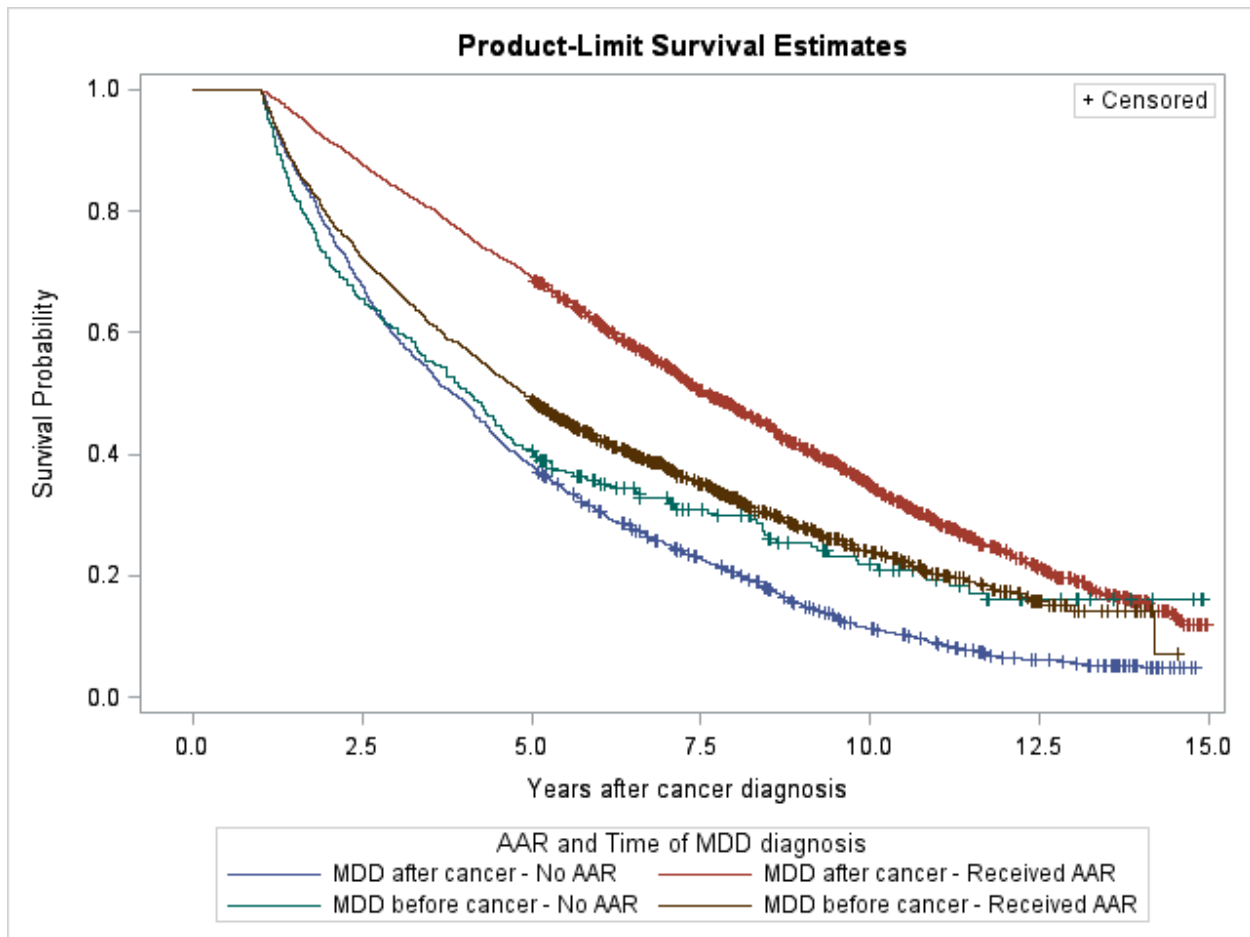
Multivariate Analyses

Impact of AAR on the Survival of Cancer Patients with MDD: Adjusted Cox proportional hazards regression showed that those who received AAR had 42% lower risk of death (HR 0.58; 95% CI 0.54-0.62) than those who did not receive AAR (results not shown). However, when an interaction between AAR and time of MDD diagnosis was included in the analysis, the impact was significant only for patients whose MDD was diagnosed after cancer (HR 0.51; 95% CI 0.47-0.55) (Table 3).

Table 3

Adjusted impact[*] of AAR on the survival of cancer patients aged ≥ 65 years with MDD who survived at least a year following cancer diagnosis

Variable	HR	95% CI	
Impact of AAR by time of MDD diagnosis			
Before cancer diagnosis (AAR Yes vs No)	0.89	0.76	1.04
After cancer diagnosis (AAR Yes vs No)	0.51	0.47	0.55
Age	1.05	1.04	1.05
Sex			
Male	ref		
Female	0.79	0.72	0.85
Ethnic concentration quintile			
Q5	ref		
Q1	0.98	0.87	1.10
Q2	1.07	0.95	1.19
Q3	1.05	0.94	1.17
Q4	0.99	0.89	1.11
Neighborhood income quintile			

Q5	ref		
Q1	1.06	0.95	1.17
Q2	1.05	0.95	1.18
Q3	1.10	0.98	1.22
Q4	1.05	0.94	1.17
Rural			
No	ref		
Yes	1.01	0.92	1.12
Cancer type			
Other	ref		
Breast	0.84	0.73	0.96
Colon and Rectum	0.85	0.75	0.96
Digestive System, except Colon and Rectum	1.33	1.13	1.57
Female Genital	1.00	0.83	1.20
Hematological	1.04	0.91	1.19
Lung and Bronchus	1.64	1.44	1.88
Prostate	0.63	0.55	0.72
Urinary system	0.95	0.82	1.09
Cancer stage at diagnosis			
I	ref		
II	1.22	1.07	1.38
III	1.68	1.46	1.93
IV	2.43	2.06	2.87
Unknown	1.19	1.06	1.33

Number of comorbidities other than MDD			
< 4	ref		
≥ 4	1.03	0.95	1.11

*Result of Cox proportional hazards regression with the interaction term between AAR and time of MDD diagnosis and confounding variables included in the model

On further examination, it was found that of the 42.6% patients whose MDD was diagnosed after cancer and did not receive AAR, 22.9% did not survive for 180 days after MDD diagnosis. Hence, unless they had an outpatient diagnosis of MDD before the hospital diagnosis of MDD, they were not in the study long enough after their MDD diagnosis to complete 180 days' continuous antidepressant refill. Sensitivity analysis was conducted excluding patients who were in the study for less than a year following MDD diagnosis. Results showed that those who received AAR still had a lower risk of mortality compared to those who did not receive AAR (HR 0.87; 95% CI 0.79-0.96), although when interaction term of AAR and time of MDD diagnosis was included in the model, the impact was significant only for patients whose MDD was diagnosed after cancer (HR 0.86; 95% CI 0.76-0.98).

Impact of AAR on the Survival of Cancer Patients with MDD according to Cancer Type: Result of adjusted Cox regression stratified by cancer type showed that for all types of cancer, those who received AAR had a lower risk of mortality than those who did not receive AAR, although the impact was not significant for cancer of digestive system, except colorectal (Table 4). The impact was highest for urinary system cancer (HR 0.43; 95% CI 0.33-0.55). Having ≥ 4 comorbidities was associated with better survival in patients among digestive system, except colorectal, (HR 0.52; 95% CI 0.38-0.71) and lung and bronchus (HR 0.76; 95% CI 0.60-0.97) cancers. Only digestive system cancer except colorectal showed a statistically significant

difference in the impact of AAR on survival compared to hematological, prostate, and urinary system cancers. In all other cancer types the confidence intervals overlapped suggesting that the impact of AAR on survival was similar.

When the interaction between AAR and time of MDD diagnosis was included in the model, in digestive system cancers (except colorectal), among patients whose MDD was diagnosed before cancer, AAR was associated with higher risk of death (HR 2.10; 95% CI 1.09-4.07), and in patients whose MDD was diagnosed after cancer, AAR was associated with a lower risk of death (HR 0.67; 95% CI 0.47-0.96). In lung cancer patients, AAR was associated with lower risk of death irrespective of time of MDD diagnosis and there was no statistically significant difference in the impacts of AAR on survival between patients whose MDD was diagnosed before cancer and patients whose MDD was diagnosed after cancer. In all other types of cancer, the impact of AAR on survival was not significant in patients whose MDD was diagnosed before cancer and AAR was associated with lower mortality risk in patients whose MDD was diagnosed after cancer.

Table 4

Adjusted impact[*] of AAR on the survival of cancer patients aged ≥ 65 years with MDD who survived at least a year following cancer diagnosis, by cancer type

Cancer type	HR	95% CI	
Breast[abg]	0.59	0.48	0.73
Impact of AAR by time of MDD diagnosis[†]			
Before cancer diagnosis (AAR Yes vs No)	0.86	0.53	1.38
After cancer diagnosis (AAR Yes vs No)	0.53	0.42	0.67
Colon and Rectum[abdeg]	0.62	0.52	0.75
Impact of AAR by time of MDD diagnosis[†]			

Before cancer diagnosis (AAR Yes vs No)	0.81	0.53	1.22
After cancer diagnosis (AAR Yes vs No)	0.58	0.47	0.71
Digestive System, except Colon and Rectum[ch]	0.89	0.66	1.20
Impact of AAR by time of MDD diagnosis[†]			
Before cancer diagnosis (AAR Yes vs No)	2.10	1.09	4.07
After cancer diagnosis (AAR Yes vs No)	0.67	0.47	0.96
Female Genital[abg]	0.49	0.35	0.67
Impact of AAR by time of MDD diagnosis[†]			
Before cancer diagnosis (AAR Yes vs No)	1.14	0.59	2.22
After cancer diagnosis (AAR Yes vs No)	0.35	0.23	0.51
Hematological[bcdeg]	0.51	0.41	0.64
Impact of AAR by time of MDD diagnosis[†]			
Before cancer diagnosis (AAR Yes vs No)	0.82	0.45	1.52
After cancer diagnosis (AAR Yes vs No)	0.46	0.36	0.59
Lung and Bronchus[abdgh]	0.57	0.46	0.71
Impact of AAR by time of MDD diagnosis[†]			
Before cancer diagnosis (AAR Yes vs No)	0.65	0.44	0.96
After cancer diagnosis (AAR Yes vs No)	0.53	0.41	0.69
Other[bcg]	0.55	0.46	0.66
Impact of AAR by time of MDD diagnosis[†]			
Before cancer diagnosis (AAR Yes vs No)	0.72	0.50	1.06
After cancer diagnosis (AAR Yes vs No)	0.50	0.40	0.62
Prostate[bg]	0.53	0.44	0.63
Impact of AAR by time of MDD diagnosis[†]			
Before cancer diagnosis (AAR Yes vs No)	0.77	0.50	1.17

After cancer diagnosis (AAR Yes vs No)	0.48	0.39	0.59
Urinary System[abcg]	0.43	0.33	0.55
Impact of AAR by time of MDD diagnosis[†]			
Before cancer diagnosis (AAR Yes vs No)	0.66	0.36	1.23
After cancer diagnosis (AAR Yes vs No)	0.39	0.29	0.52

[*]Result of Cox proportional hazards regression stratified by cancer type and adjusted for time of MDD diagnosis, age, sex, ethnic concentration quintile, neighborhood income quintile, rural, cancer stage at diagnosis, and number of comorbidities other than MDD

[†]Result of Cox proportional hazards regression, stratified by cancer type, with the interaction term between AAR and time of MDD diagnosis and the confounders (age, sex, ethnic concentration quintile, neighborhood income quintile, rural, cancer stage at diagnosis, and number of comorbidities other than MDD) included in the model

[a]p<0.05 for time of MDD diagnosis

[b]p<0.05 for age

[c] p<.05 for sex

[d]p<0.05 for ethnic concentration quintile

[e]p<0.05 for neighborhood income quintile

[g]p<0.05 for cancer stage

[h]p<0.05 for number of comorbidities other than MDD

Discussion

This study evaluated whether adequate antidepressant refill defined as 180 days' continuous refill of antidepressants, had an impact on the survival of older cancer patients with a hospital discharge diagnosis of major depressive disorder. MDD was diagnosed after cancer diagnosis for a majority of the sample (67.6%). It suggests that increased stress associated with

cancer diagnosis may lead to MDD. Alternatively, it may also be due to increased screening for MDD in patients after cancer diagnosis, since the clinical practice guidelines by Cancer Care Ontario recommends screening all cancer patients for depression (Li et al., 2016).

A higher proportion of patients received AAR when their MDD was diagnosed before cancer compared to patients whose MDD was diagnosed MDD after cancer. However, this was mainly because in patients whose MDD was diagnosed after cancer, 22.9% died before 180 days of MDD diagnosis. In addition, after cancer diagnosis, antidepressants may not be prescribed to avoid disease progression (Christensen et al., 2016) and interactions with cancer drugs (Desmarais & Looper, 2009). It should also be noted that fewer patients diagnosed with later stages of cancer received AAR compared to patients diagnosed with earlier stages of cancer. In end-stage cancer patients, antidepressants may not be prescribed because they typically take four to six weeks to start showing benefits and have side effects that are particularly risky for such patients (Johnson, 2018). Instead, psychostimulants, and alternative treatments such as electroconvulsive therapy and herbal remedies are used for treating depression in end-stage cancer patients (Johnson, 2018).

The results showed that those who received AAR had a lower risk of mortality when compared to those who did not receive AAR; however, the overall impact of AAR on cancer survival was significant only for patients diagnosed with MDD after cancer diagnosis. The results are in alignment with our assumption that proper management of MDD can lead to better health-related behaviours and as a result lead to better survival. In patients whose MDD was diagnosed before cancer, AAR might have resulted in a better control of MDD by the time of cancer diagnosis, and hence the impact of AAR on cancer survival might have been attenuated. Kaplan-Meier curves showed that patients whose MDD was diagnosed after cancer and did not

receive AAR had the lowest survival. Those patients might have had a poor survival prognosis due to cancer characteristics and that might have been the reason why they did not receive antidepressants in the first place.

A recent study in Israel found that adherence to antidepressants is associated with reduced risk of mortality in patients (Shoval et al., 2019). The study calculated adherence by dividing the duration of purchase of antidepressants by duration of continuous prescription of antidepressants and considered those who scored below 20% as nonadherent. However, that study did not find any impact of antidepressant adherence on colon cancer survival (Shoval et al., 2019) whereas our study found that colorectal cancer patients with MDD who received AAR had 38% lower risk of death than those who received AAR. A similar study among patients with depression following myocardial infarction also showed that those who were treated with antidepressants had a lower risk of death compared to those who were not treated with antidepressants (Taylor et al., 2005). Their sample included patients with dysthymia, major depression, or minor depression (Taylor et al., 2005) whereas our study included patients with hospital diagnosis of MDD only, which given the severity of other presenting diagnoses, may be identified only when it is severe.

An interesting finding was that for all types of cancers except digestive system other than colorectal and lung and bronchus, the impact of AAR on survival was not significant if MDD was diagnosed before cancer. Surprisingly, in patients with digestive system cancers other than colorectal, AAR was found to be associated with higher risk of death if MDD was diagnosed before cancer. Liver toxicity associated with antidepressant use in the older patients may be one of the reasons for the increased mortality associated with AAR in those patients (de Gage et al.,

2018). AAR had a positive impact on the survival of all cancer types if the MDD was diagnosed after cancer diagnosis.

Contrary to the studies that have shown increased mortality in breast cancer patients associated with antidepressant use (Busby et al., 2018; Wernli et al., 2011), our study showed that AAR had a protective effect on breast cancer survival, especially among patients with MDD diagnosed after cancer. The difference between our study and theirs is that they compared antidepressant users and non-antidepressant users in samples that included cancer patients with or without depression (Busby et al., 2018; Wernli et al., 2011) whereas our sample included cancer patients with MDD only and compared those who received AAR and those who did not receive AAR. In lung cancer patients, antidepressant use was found to be associated with better survival by a study in the USA (Zingone et al., 2017). However, that study did not ascertain whether the participants had depression or not and hence might have included lung cancer patients with or without depression. (Zingone et al., 2017).

Number of comorbidities other than MDD was not a significant predictor when considering all cancer types together. However, stratified analysis by cancer type found that patients with < 4 comorbidities had higher risk of death than patients with ≥ 4 comorbidities for digestive system except colorectal and lung and bronchus cancers. The positive association between number of comorbidities and survival may be due to reverse causality when those who lived longer developed more chronic conditions later in their life. It should be noted that lung and bronchus cancer patients had the second highest mortality (Table 1) and digestive system except colorectal had the lowest percentage of patients receiving AAR (Table 2). In older cancer patients it has been shown that in general comorbidities are associated with poorer survival

(Galvin et al., 2018), although some studies have failed to show any such impact (Antonio et al., 2017).

Diagnosing depression in older cancer patients is challenging because they may not acknowledge depressed mood and anhedonia, which are the main diagnostic symptoms for depression, and because the physical symptoms of cancer and old age such as fatigue, aches and pain, and sleep problems are similar to the physical symptoms exhibited by depressed patients (Weinberger et al., 2011). They are also less likely to be referred to specialized psychosocial care as evidenced by a study that showed that only 22% of patients aged ≥ 70 years were referred compared to 100% of patients aged ≤ 40 years (Ellis et al., 2009). The findings of this study provide evidence supporting the importance of proper diagnosis and management of depression in older cancer patients.

Limitations

This study assumed that since individuals ≥ 65 years are eligible for ODB drug coverage, details regarding their antidepressant use can be obtained from the ODB database. However, patients whose MDD was diagnosed before they turned 65 years old might not have been covered by ODB at the time of MDD diagnosis in which case their antidepressant use could not be identified from the ODB database. Therefore, there is a possibility that some of the patients who were identified as not having received AAR had received antidepressants either via private drug insurance or by paying from their own pockets, resulting in misclassification bias. This might have resulted in underestimation of the impact of AAR on survival. There is also the possibility that patients who did not receive AAR received non-medicinal management of MDD, which also would have attenuated the impact of AAR on survival. The results of sensitivity analysis showed that the analysis excluding patients who died within one year of MDD diagnosis

resulted in a lower estimate of risk of death (HR 0.87; 95% CI 0.79-0.96). This shows that our study might have reverse causality issues.

We included only hospital-discharge diagnosis of MDD as the inclusion criteria, which excluded patients with outpatient diagnosis of MDD and milder forms of depression from participating in the study. Hence the results may not be generalizable for all older cancer patients with depression. Since the study was done in patients aged $\geq$ 65 years, the estimates may be different for younger cancer patients.

Strengths

Since this is a population-based study, which included all patients with cancer and MDD who were $\geq$ 65 years old and survived a year or more after cancer diagnosis in Ontario, it minimizes selection bias and facilitates decision-making better than studies on smaller samples. This study has a relatively long follow-up period (5.8 years in average), which allowed assessment of the impact of adequate antidepressant refill over a longer time period. Stratified results by cancer type showed the importance of AAR in improving the survival in all types of cancer patients and suggests that cancer patients with depression have worse survival outcomes in the absence of AAR.

Conclusions

Among older cancer patients with depression, adequate antidepressant refill had a protective effect on cancer survival, especially in patients whose depression was diagnosed after cancer diagnosis. To our knowledge, there have not been any studies in the past that examined the impact of antidepressant therapy on the survival of depressed cancer patients. Past studies have only compared cancer patients who used antidepressants and those who did not use antidepressants in samples including both depressed and nondepressed cancer patients. This

study demonstrates the scope of adequate antidepressant therapy in improving the survival of older cancer patients with depression. It shows that health care providers should give importance to depression and other mental health issues while creating a treatment plan for cancer patients, especially in the older age group. Extending insurance coverage for prescription drugs for younger (<65 years old) cancer patients may be beneficial for their adherence to antidepressants.

Studies including patients with outpatient diagnosis of depression and/or of younger age group should be conducted to ascertain that the results of this study are generalizable for all cancer patients. Further studies are needed to examine the impact of other types of treatment for depression in cancer patients. The results also justify further research on access to mental health treatment for cancer patients in Canada.

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Appendix A

ICES databases used for obtaining data for the study

Database	Description	Variables
Discharge Abstract Database (DAD)	Information on hospitalizations in Ontario. Includes admissions, length of stay and discharges.	Major depressive disorder using the diagnosis codes, time of diagnosis
Ontario Cancer Registry (OCR)	Information on all Ontario residents diagnosed with cancer. Includes date of diagnosis, site of primary cancer and cancer deaths.	Age at diagnosis, sex, primary cancer site, stage at diagnosis, time of death
Ontario Health Insurance Plan (OHIP) claims database	Information on claims paid for by OHIP. Includes physician visits, hospitalizations and associated diagnosis.	Comorbidities including depression using the diagnostic codes, time of diagnosis
Registered Persons Database (RPDB)	Demographic information for all individuals who have ever had a valid Ontario health card number. Includes age, sex, neighbourhood income and residence.	Neighbourhood income quintile, rurality, time of death
National Ambulatory Care Reporting System (NACRS)	Information on outpatient visits to hospital and community-based ambulatory care. Includes day surgery, outpatient clinics, and emergency departments.	Comorbidities including depression using the diagnostic codes, time of diagnosis
Ontario Drug Benefit (ODB) claims database	Information about drug claims by ODB beneficiaries such as drug	Antidepressant use from DIN, time of refill, quantity dispensed

	identification number, quantity dispensed, and dispensing date	
Ontario Marginalization Index (ON-Marg)	Information regarding deprivation or marginalization based on residential instability, material deprivation, dependency, and ethnic concentration	Ethnic concentration quintile

Appendix B

List of antidepressants and their drug identification numbers

Antidepressant generic name	Drug identification number
Amitriptyline	16306
Amitriptyline HCL	37400, 335053, 335061, 335088, 654507, 654515, 2326043, 2326051, 2326078, 2429861, 2429888, 2429896
Bupropion HCL	2237824, 2237825, 2238441, 2260239, 2275074, 2275082, 2275090, 2275104, 2285657, 2285665, 2313421, 2325373, 2382075, 2382083, 2439654, 2439662
Citalopram HBR	2239607, 2239608, 2246056, 2246057, 2246594, 2246595, 2248010, 2248011, 2248050, 2248051, 2248170, 2248171, 2251558, 2251566, 2252112, 2252120, 2275562, 2275570, 2285622, 2285630, 2293218, 2293226, 2304686, 2304694, 2306239, 2306247, 2313405, 2313413, 2322781, 2322803, 2331950, 2331977, 2353660, 2353679, 2355256, 2355272, 2355280, 2371898, 2371901, 2409011, 2409038, 2429705, 2429713, 2430541, 2430568
Clomipramine	2040751, 2040778, 2040786
Clomipramine HCL	324019, 402591, 2139340, 2139359, 2139367, 2244816, 2244817, 2244818
Desipramine HCL	1946269, 1946277, 1948784, 1948792, 2216256, 2216264, 2216272, 2223325, 2223333

Doxepin HCL	24333, 24341, 1913441, 1913468, 2049996, 2050005, 2050013, 2050021, 2050048, 2050056, 2140098
Duloxetine	2301482, 2301490, 2429446, 2429454, 2440423, 2440431
Duloxetine HCL	2426633, 2426641, 2436647, 2436655, 2437082, 2437090, 2438259, 2438267, 2438984, 2438992, 2439948, 2439956, 2451913, 2451921
Escitalopram	2454297, 2454300
Escitalopram oxalate	2263238, 2263254, 2295016, 2295024, 2303949, 2303965, 2309467, 2309475, 2313561, 2313588, 2318180, 2318202, 2364077, 2364085, 2385481, 2385503, 2391449, 2391457, 2397358, 2397374, 2407418, 2407434, 2423480, 2423502, 2429780, 2429799, 2430118, 2430126, 2440296, 2440318
Fluoxetine	2286076
Fluoxetine HCL	636622, 2177587, 2216361, 2216590, 2237814, 2241374, 2242178, 2243487, 2380579, 2385635, 2386402, 2392917, 2405709
Fluvoxamine	2240682, 2240683
Fluvoxamine maleate	1919342, 1919369, 2218453, 2218461, 2231329, 2231330, 2239953, 2239954, 2247054, 2247055, 2255529, 2255537
Imipramine HCL	21504, 312797, 326852, 360201
Maprotiline HCL	2158612, 2158620

Mirtazapine	2243910, 2248542, 2248543, 2248544, 2248762, 2250608, 2256118, 2259354, 2267292, 2270927, 2274361, 2279894, 2279908, 2279916, 2286629, 2299801, 2299828, 2299836, 2352842, 2411709
Moclobemide	2218410, 2232148, 2232150, 2239747, 2239748, 2240456, 2243218
Nefazodone HCL	2087383, 2237398, 2237399, 2237400
Nortriptyline	2240789, 2240790
Nortriptyline HCL	15229, 15237, 2177692, 2177706, 2223511, 2223538, 2231686, 2231687, 2231781, 2231782
Paroxetine HCL	1940473, 1940481, 2240908, 2240909, 2247751, 2247752, 2247811, 2247812, 2248013, 2248014, 2248557, 2248558, 2254751, 2262754, 2262762, 2269430, 2269449, 2368870, 2368889. 2383284, 2411954, 2421380, 2421399, 2431785
Phenelzine sulfate	476552
Sertraline	2238280, 2238281, 2238282
Sertraline HCL	1962779, 1962817, 2132702, 2240481, 2240484, 2240485, 2242519, 2242520, 2242521, 2244838, 2244839, 2244840, 2245159, 2245160, 2245161, 2245787, 2245788, 2245789, 2273691, 2287390, 2287404, 2287412, 2353520, 2353539, 2353547, 2357143, 2357151, 2357178, 2374552, 2374560, 2374579, 2390906, 2390914, 2390922, 2399415, 2399423, 2399431, 2402378, 2402394, 2402408, 2427788, 2427796

Tranylcypromine sulfate	1919598
Trazodone HCL	579351, 579378, 702277, 1937227, 1937235, 2053187, 2053195, 2053209, 2144263, 2144271, 2144298, 2147637, 2147645, 2147653, 2231683, 2231684, 2277344, 2277352, 2277360, 2348772, 2348780
Trimipramine maleate	740799, 740802, 740810, 740829, 1940430, 2070987
Tryptophan	2230202, 2237250
Venlafaxine HCL	2103702, 2237279, 2237280, 2237282, 2273969, 2273977, 2273985, 2275023, 2275031, 2275058, 2278545, 2278553, 2278561, 2304317, 2304325, 2304333, 2310279, 2310287, 2310295, 2310317, 2310325, 2310333, 2331683, 2331691, 2331705, 2354721, 2360020, 2360039, 2360047, 2380072, 2380080, 2380099, 2452847, 2452855

Chapter 6: Discussion

The purpose of this research was to study whether the presence of depression had an impact on the survival of cancer patients in the context of multimorbidity and to examine whether adequate antidepressant use had any effect on the survival of cancer patients with depression. Results showed that major depressive disorder recognized during a hospitalization is associated with higher risk of death in cancer patients and that number of comorbidities other than depression modifies the impact of depression on survival. Another key finding was that 180 days' continuous refill of antidepressants was associated with better survival in older cancer patients whose depression was diagnosed after a cancer diagnosis.

6.1 Main Findings

6.1.1 Depression is Associated with Poorer Cancer Survival

The study results showed that cancer patients who had MDD had 58% higher risk of death than cancer patients without MDD when adjusted for all other covariates included in the study. This confirms our hypothesis that MDD has an impact on the survival of cancer patients. Other studies on the impact of depression on cancer survival have shown similar results (Chang et al., 2014; Prasad et al., 2014b; Prieto et al., 2005). A very recent population-based study in South Korea also found that pre-existing depression diagnosed within two years before cancer diagnosis was associated with 60% higher risk for mortality (A. Ko et al., 2019). In all types of cancer, depression increased the risk of death. Past studies on lung cancer (Vodermaier et al., 2017) and breast cancer (Vodermaier et al., 2014) patients in Canada have found similar association between depression and cancer mortality.

Impact of MDD on survival was higher in patients with cancer types that have longer survival and lower in patients with cancer types that have shorter survival. In cancer's with longer survival, MDD has a longer time to influence the patient's lifestyle and quality of life

resulting in the higher impact of MDD on survival in patients with those types of cancers compared to patients with cancer types that have shorter survival.

Interestingly, the impact of depression was higher in the younger (< 65 years) age group compared to the older age group. The reason might be because older cancer patients might have other severe comorbidities that affect their survival more than depression. Another explanation is better coordinated care in older patients due to the involvement of geriatricians, which decreases the impact of depression on survival.

6.1.2 Number of Comorbidities Modify the Impact of Depression on Cancer Survival

The impact of depression on cancer survival was higher in patients with fewer comorbidities. This might be because severity of other comorbidities had a greater impact on survival than depression in patients with more comorbidities. However, since the impact of MDD on survival was statistically significant at all levels of multimorbidity, it is important to identify and treat depression in all cancer patients to improve their survival.

6.1.3 Adequate Antidepressant Refill is Associated with Better Survival in Cancer Patients with Depression

Older (65 years and older) cancer patients with MDD diagnosed after cancer had higher chances of survival if they had 180 days' continuous refill of antidepressants. The impact was statistically significant for all types of cancer. This result supports our hypothesis that adequate treatment of depression can result in improved survival of cancer patients with depression. AAR did not have an impact on the survival of older cancer patients whose MDD was diagnosed before cancer. This may be because MDD was well controlled before cancer diagnosis in those patients. Number of comorbidities did not have an impact on the survival of cancer patients with depression aged 65 years or more.

All covariates except rurality of residence were statistically significant predictors of overall mortality in cancer patients. This is similar to other studies conducted in Canada that found no rural/urban disparity in cancer survival (Canale et al., 2018; J. D. Kim et al., 2018). Those studies attribute the lack of rural/urban disparity to the publicly funded health care system in Canada, which ensures accessibility of health care to all residents (Canale et al., 2018; J. D. Kim et al., 2018). Income was a significant predictor of survival for the entire cohort, although for the older patients with depression, income was not statistically significant. Patients residing in neighborhoods with high-income had a better survival when compared to patients residing in low-income neighborhoods. This is similar to the findings of past studies in Canada (C. Boyd et al., 1999; McDonald et al., 2014).

Similar to other studies (Ellison, 2016; Kinoshita et al., 2017; Radkiewicz et al., 2017), our results also showed that female cancer patients had better survival than males. Patients residing in locations with high concentration of recent immigrants had higher survival rates than patients from neighborhoods with lower concentration of recent immigrants. This corroborates the study by Cheung et al. (2017), which showed that immigrants have better cancer survival than Canadian-born patients. Prospective immigrants must undergo medical clearance for immigration, hence only relatively healthy individuals immigrate to Canada. Canada selects immigrants based on their education and skills, which also might influence their health outcomes.

6.2 Limitations

Misclassification bias related to administrative data is the main limitation of this study. Trustworthiness of administrative data depends on data completeness and accuracy of coding (Fortin et al., 2012). Patients may have outpatient diagnosis of MDD, which was not identified

by this study, leading to an underestimation of MDD prevalence. Hospitalized cancer patients have a high risk of death (Numico et al. 2015) and hence diagnosis of MDD in hospitalized patients implies that MDD is diagnosed in patients with higher likelihood of death. Hence, this study might have differential misclassification bias where patients who are likely to have the outcome are more likely to have been identified as exposed, resulting in overestimation of the impact of MDD on survival and reverse causality. Depression is recognized as a diagnosis during hospitalizations only in patients with severe depression, which also could have led to overestimation of the impact of MDD on survival.

Although depression is managed with psychotherapy in addition to antidepressants, information regarding psychotherapy is not available from OHIP databases since it is not covered by OHIP. Hence, we do not know whether the study participants received psychotherapy. Since patients included in the non-exposed group (who did not receive AAR) in pat 2 of the study could have had their depression managed by non-medicinal methods, the resulting misclassification bias would have resulted in an underestimation of the impact of AAR on survival. The significantly lower HR estimates when the patients who died within a year of MDD diagnosis were excluded from the analysis signifies that there could be potential reverse causality bias in the second part of the study.

Patients may have other chronic diseases which were not included in this study and hence the number of comorbidities might have been underestimated. Severity of comorbidities may impact survival more than number of comorbidities. Not considering severity of comorbidities when calculating level of multimorbidity is another limitation of this study. Health behaviours such as smoking, physical exercise, and alcohol use are important factors that influence survival; however, due to limitations of data availability they were not included as confounders.

6.3 Strengths

The first part of the study included all adults in Ontario who were diagnosed with cancer during the index period and hence analysed a large population-based data. The second part also included all Ontario residents diagnosed with cancer at age ≥ 65 years and had a hospital diagnosis of MDD. Population-based estimates can inform decision-making better than studies on small samples. The follow-up period is long, 7.5 years for the first part including all adult cancer patients and 5.8 years for the second part including cancer patients aged ≥ 65 years with a hospital diagnosis of MDD, which allowed the assessment of longer-term survival among cancer patients. Since provincial-level data were analysed, selection bias was minimum. Multiple types of cancer were included in this study and stratified analyses showed the impact of depression and adequate antidepressant refill on the survival of different types of cancer.

6.4 Epidemiological Implications: Internal Validity/External Validity

Since we identified depression only in hospitalized patients having a diagnosis of major depression, we most certainly underestimated the prevalence of depression. The specificity of the study in identifying MDD was high since the patients diagnosed with MDD during hospitalizations would be severely depressed and there is low likelihood of patients without MDD being identified as depressed. However, since some patients classified as not having MDD might have had MDD diagnosed in outpatient settings, the study might have been less sensitive in identifying MDD. As a result, the estimated impact of MDD might have been less than what would have been if all cases of MDD were identified. The prevalence of MDD estimated by this study is 2%, which is much lower than the annual prevalence of major depression in Canada, 5% (Patten et al., 2016).

For the second part of the study, we might have included some patients who received adequate antidepressant refill in the group that did not receive adequate antidepressant refill if their MDD was diagnosed before they turned 65 years old and became eligible for ODB. If all patients who received AAR were identified correctly, the HR estimates might be higher than what we have calculated.

Since this is a population-based study, with minimal selection bias, and the analyses adjusts for the main confounders, the internal validity is high. External validity is also high and the results may be applicable for the rest of Canada and high-income countries with a similar population. However, the contextual factors mentioned in the Andersen model (Andersen, 1995) should be considered when applying the study results. Social and cultural characteristics and health beliefs can vary in different populations and hence the estimates may differ for specific communities. Access to mental health care may differ in countries where there is high stigma around mental health. Treatment approaches for depression may also be influenced by the characteristics of the health systems and society. In Canada, the impact of depression on survival can be higher among Indigenous people than our population-level estimates due to the mediating factors such as poor access to care (Lavoie et al., 2016), low quality of care, and racial stereotyping (Browne & Fiske, 2001). A high percentage of indigenous people live on reserves (Statistics Canada, 2018b), which also can be an obstacle to accessing care and impact their survival.

We compared patients with a hospital discharge diagnosis of MDD and those without a hospital discharge diagnosis of MDD. Therefore, the results may not be sufficiently relevant for those with milder forms of depression. For the second part studying the impact of antidepressants, only patients who were ≥ 65 years old at the time of cancer diagnosis and had a

hospital diagnosis of MDD were included. Hence, the results are applicable for that age group only. Validity of the results of stratified analysis by type of cancer in part 2 is limited because of smaller number of patients in each category (For example, n=240 for digestive system cancers except colorectal, among whom only 32 were alive).

Chapter 7: Conclusion: Summary/Implications/Future directions

The results of this population-based study in Ontario showed that depression is associated with shorter survival in cancer patients and the impact of depression on survival changes according to number of other chronic diseases in a cancer patient. The study also showed that, among older cancer patients with depression, adequate antidepressant refill is associated with decreased mortality, specifically in patients whose MDD was diagnosed after cancer. The results encourage health care providers to identify depression in cancer patients, provide adequate treatment/prescribe appropriate medication, and to promote adherence to depression treatment to improve cancer survival.

In all types of cancer, MDD was associated with shorter survival and in all types of cancer patients with MDD, AAR was associated with better survival. Although the impact of MDD on survival was smaller for cancers with poorer prognosis, the finding that there still was an impact stresses that it is important to identify and treat depression in all types of cancer. Appropriate treatment of depression can improve the quality of life of cancer patients with depression (Fisch et al., 2003), which is crucial even if the duration of survival is less.

In Ontario, the Ontario Health Insurance Plan (OHIP) provides coverage for hospitalizations and doctors' visits for all residents, but drugs prescribed in non-hospital settings are not covered (Ontario, 2020b). OHIP+ provides prescription drug coverage for residents under 25 years of age if they do not have private insurance (Ontario, 2017) and Ontario Drug Benefits plan provides prescription coverage for adults aged 65 or more. Adults between 25 and 65 years of age are not covered for prescription drugs by the provincial health insurance programs (Ontario, 2020b). Extending drug coverage to all age groups may improve access and adherence to antidepressants, since individuals without drug insurance may not adhere to medications due to cost-related issues (Law et al., 2012).

This study showed that depression had an impact on the survival of patients with cancer, which is a chronic disease. Mental health conditions may go undiagnosed in patients with chronic conditions. The results of this study may be applicable to patients with or without other chronic diseases. Therefore, identifying depression and other mental health issues in individuals and providing adequate treatment is important for the health of the population. Public health measures for improving access to mental health care should be promoted.

Future studies should identify the impact of minor depression and depression diagnosed in outpatient as well as inpatient settings on cancer survival. Impact of antidepressants in younger cancer patients with depression should also be studied. Identifying the factors associated with adequate antidepressant refill can assist in developing programs for improving treatment compliance in cancer patients. Studies on non-medicinal management of depression and their impacts on outcomes in cancer patients will help to determine the best methods in managing depression in cancer patients. Mental illnesses and their influence on other outcomes such as quality of life and quality-adjusted life years may also be studied. The results also justify further research on access to mental health treatment for cancer patients in Canada. Research investigating the effect of depression and other mental heath disorders on the survival and other outcomes in patients with other chronic diseases should also be encouraged.

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