Investigating variations in survival rates for women diagnosed with ovarian cancer in Nova Scotia

by

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Dalhousie is located in Mi'kma'ki, the
ancestral and unceded territory of the Mi'kmaq
We are all Treaty people.

Dedication

For my Aunt Colleen, taken from us far too soon by ovarian cancer. This thesis is dedicated to her memory, as she has been my guiding inspiration to make a meaningful impact on the fight against this disease.

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Abstract

Introduction: Globally, ovarian cancer is the 6th most common type of cancer among women. Though advancements in early detection and treatment practices continue to improve cancer outcomes, only about half of women who are diagnosed with ovarian cancer will survive 5 years. There is large inter- and intra-country variability in ovarian cancer outcomes. Individuals diagnosed with advanced stage cancer in Nova Scotia have a 3-year net survival of 31.9%, which is the lowest in the country. This study aimed to identify prognostic factors impacting survival throughout Nova Scotia, and to investigate if there is evidence of inequities in both survival and access to care from the point of diagnosis, based on geographical regions, poverty, mental illness, or continuity of care.

Methods: This study utilized a population-based retrospective design of all women diagnosed with ovarian cancer in Nova Scotia from Jan 1, 2007 to Dec 31, 2016. Cancer registry, clinical, and administrative health data were linked to gather data on individual, tumor, treatment, regional, and health system characteristics. Both illegitimate and legitimate prognostic factors potentially contributing to regional variations and inequities in ovarian cancer survival were assessed using time to event (i.e., survival analyses) techniques. Logistic regression models were used to determine which of these factors were associated with inequities in access to specialist care, including surgery at a tertiary care hospital and assessment by a gyne-oncologist within 6 months of diagnosis.

Results: This study found no regional differences in survival across Nova Scotia. Furthermore, it revealed that disparities in illegitimate prognostic factors do not appear to be significantly associated with survival outcomes at the time of diagnosis. Instead, survival variations were primarily attributed to legitimate prognostic factors, such as cancer stage, subtype, comorbidities, and frailty. However, notable inequities were identified in accessing specialist care, which substantially influenced survival time. Just under one-quarter of the study population were not assessed by a gyne-oncologist within 6 months of diagnosis. While survival was associated with surgery location, a significant proportion of individuals did not undergo surgical intervention, and demographic differences were observed between these groups.

Conclusion: Though inequities do not appear to be contributing to differences in ovarian cancer survival at the time of diagnosis within Nova Scotia, they may indirectly influence outcomes by limiting access to specialist care. This highlights the need for targeted interventions and policy change at the system level to ensure that all women in Nova Scotia are assessed by gyne-oncologists in a timely manner, to ensure they can choose the most appropriate management strategy and potentially have an improved chance at survival.

List of Abbreviations and Symbols Used

X^2	Chi-Squared
CFS	Clinical Frailty Scale
CI	Confidence Interval
DAD	Discharge Abstract Database
EFS	Edmonton Frailty Scale
EGROUP	Eligibility Group Database
HR	Hazard Ratio
HDNS	Health Data Nova Scotia
ICBP	International Cancer Benchmarking Partnership
LOC	Lifetime Ovulatory Cycles
MSI	Medical Services Insurance
NICE	National Institute for Health and Care Excellence
NACT	Neo-Adjuvant Chemotherapy
NSCR	Nova Scotia Cancer Registry
NSH	Nova Scotia Health
OR	Odds Ratio
PFI	Platinum Free Interval
PH	Proportional Hazards
REB	Research Ethics Board
SES	Socio-Economic Status
SE	Standard Error
UPC	Usual Provider Continuity

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Chapter 1: Introduction

Globally, ovarian cancer is the 6th most common type of cancer among women and the deadliest type of gynaecological cancer, largely because of the lack of early detection methods.[1,2] The disease makes up 1.6% of cancer cases and 1.9% of cancer deaths worldwide.[1] Though advancements in early detection and treatment practices continue to improve cancer outcomes generally, developments within ovarian cancer are not keeping pace. Only about half of women who are diagnosed with ovarian cancer will survive 5 years.[3] The poor prognosis is heightened by the fact that 70% of women with ovarian cancer are diagnosed at a late stage.[4] The International Cancer Benchmarking Partnership (ICBP) has demonstrated that ovarian cancer survival differs between countries, with Canada being in the middle of the pack.[5] These survival rates have also been found to vary between Canadian provinces; for example, for women diagnosed with advanced stage disease, 3-year survival ranges from 31.9% in Nova Scotia to 38.6% in Alberta.[4] Due to a lack of research, it is largely unknown why these differences exist. The ICBP has determined that the frequencies of major prognostic factors, such as the stage at diagnosis, remain relatively constant throughout Canada and worldwide.[4] So, what is it about Nova Scotia that leads to a poorer survival for women diagnosed with ovarian cancer? The aim of this research was to start to answer this question by first analyzing the prognostic factors that may be contributing to potential regional variations in survival and to identify inequities in both survival and access to care, from the point of diagnosis.

No prior study has examined this issue in Canada. In fact, little health services research has been done on ovarian cancer in Canada at all, highlighting the importance of this research. With no understanding of why variations in survival exist, it is impossible

for policymakers, healthcare providers, and researchers to intervene to ensure all women receive timely access to gold-standard care and the best chance at survival. To ensure the results will be directly utilized within the health care system, this research was done in close collaboration with gynecologic oncologists in Nova Scotia. We hope that this study will help us better understand why differences exist for ovarian cancer outcomes in our province, and lead to interventions to improve outcomes and reduce inequities.

Research Objectives

It is increasingly important for research to fill the knowledge gap in ovarian cancer survival variations to ensure that women diagnosed with the disease in Nova Scotia are given equitable access to proper healthcare. The critical steps in achieving this goal, and the primary objectives of this study, are to identify which prognostic factors are associated with potential regional variations in survival throughout Nova Scotia, and to identify any potential inequities in both survival and access to care, at the point of diagnosis going forward. These objectives are summarized as follows:

Objective 1: To determine which prognostic factors are contributing to potential regional variations in survival within Nova Scotia, and to identify any potential inequities associated with survival, from the point of diagnosis.

Objective 2: To assess if equitable access to health care, such as being seen by a gyne-oncologist and surgery at a tertiary hospital, impacts ovarian cancer survival from the point of diagnosis, and to determine which prognostic factors are associated with differences in access to specialist care.

Methods

This study utilized a population-based retrospective design of all women

identified from the Nova Scotia Cancer Registry who were diagnosed with ovarian cancer from January 1st, 2007 to December 31st, 2016. These data were linked to a database held by the Division of Gynecological Oncology at Dalhousie University and multiple administrative health datasets held by Health Data Nova Scotia to gather data on individual, health system, and tumor characteristics. Descriptive data were analyzed for all characteristics to determine how they vary across the province in terms of frequency and prevalence. Time to event (e.g., survival analysis) techniques were used to examine which prognostic factors were associated with variations in ovarian cancer survival from the point of diagnosis, and to identify potential inequities in survival. Finally, logistic analysis techniques were utilized to determine which factors were associated with inequities in access to specialist care.

Integrated Knowledge Translation

This research has been done in close collaboration with the team of gynecologic oncologists in Nova Scotia. Not only will this ensure that the results will be directly utilized within the health care system, but it allows for the work to be done in an environment that is closely affiliated with policymaking. We were able to directly provide information about areas in the healthcare system and the province itself that could benefit from change in a way that is clear, tangible, and actionable. In addition, we will continue working with patient advocacy organizations such as Ovarian Cancer Canada in the hopes that they can help interpret the results of this study to bring about system change that is important at the patient level.

Chapter 2: Background and Literature Review

2.1 The Burden of Ovarian Cancer

2.1.1 What is Ovarian Cancer?

Globally, ovarian cancer is the 6th most common type of cancer among women and the deadliest type of gynaecological cancer.[1] This is largely due to the lack of early detection methods, meaning most women present with advanced stage disease.[2] It makes up for 1.6% of cancer cases and 1.9% of cancer deaths worldwide.[1] International studies have demonstrated that ovarian cancer survival trends differ between countries, with Canada in the middle of the pack.[5] In 2021, Canada's incidence rate of ovarian cancer was 13.5 per 100,000 individuals; an estimated 3000 Canadian women were diagnosed with ovarian cancer, and an estimated 1950 died from the disease.[3] Survival rates also vary between Canadian provinces; for example, for women diagnosed with advanced stage disease (i.e. stage III and IV), 3-year survival ranges from 31.9% in Nova Scotia to 38.6% in Alberta.[4] Due to a lack of research, it is unclear why these differences exist despite limited variation in age and stage distribution throughout the country.

More than 90% of ovarian cancer cases are epithelial carcinomas.[6] The remainder of cases are made up of germ cell and sex-cord stromal carcinomas, but these are very rare and were not the focus of this study.[7] Epithelial ovarian cancer is further differentiated into additional sub-types: high-grade serous, low-grade serous, endometroid, clear cell, mucinous carcinomas, and small number of other rare histologies (e.g. carcinosarcoma, transitional cell, etc.).[8,9,10] High-grade serous carcinomas make up the majority of cases and unfortunately have the poorest survival as around 80% of patients are diagnosed at a late stage.[11] Though these sub-types are distinct, the

classification system has been critiqued as oversimplified as they are often considered and treated similarly.[12,13] Symptoms of ovarian cancer are non-specific and, when present, indicative of advanced stage disease.[14] These may include abdominal distension and pain, changes in bowel or bladder habits, or gynaecological complaints.[6] These symptoms may greatly affect quality of life, so referral to palliative care for symptom management is important.[15]

2.1.2 Who Does it Impact?

Ovarian cancer is most often considered an age-related disease as there is increasing incidence and mortality with increasing age, with the highest incidence in those aged 70-74.[16] The mean age at diagnosis in Canada is 63, though this may vary by sub-type and stage at diagnosis.[4] The etiological risk factors for developing ovarian cancer are largely unknown and appear to vary by sub-type. Genetic cases make up about 20-25% of cases and are most commonly caused by mutations in the BRCA1 and BRCA2 tumour suppressor genes (13-18% of cases in North America), but may also be caused by mutations in other genes such as those associated with Lynch Syndrome.[17,18,19] Additionally, women with a first degree relative affected by ovarian cancer, who is not a carrier of the BRCA gene, have a 30% risk of developing ovarian cancer.[20] There have been a small number of studies that have determined an increased risk of ovarian cancer in those that have endometriosis, though the mechanisms are not well understood.[21,22]

Several reproductive and hormonal factors have been found to have a protective effect against ovarian cancer, most predominantly having higher parity of births and the use of oral contraception.[2] This is because there is an increased risk of ovarian cancer with increasing lifetime ovulatory cycles (LOC), so factors that supress ovulation, such as

pregnancy and the use of hormonal birth controls, will mediate this association.[23] A study by Trabert et al found that those in the 90th percentile of LOCs (>514) had almost twice as much of a risk of being diagnosed with ovarian cancer compared to women in the 10th percentile (<294).[23] Use of LOC repressors such as oral contraception have been found to reduce the risk of ovarian cancer for over 30 years after ceasing use.[24]

2.1.3 Prognosis

Though the incidence and mortality rates of ovarian cancer are slightly improving over time, developments are not happening at the same pace as other cancers and disparities continue to persist.[25,26,27] Treatments for ovarian cancer are rarely considered curative and most women will relapse and require multiple lines of treatment, eventually dying from the disease.[28,29,30] Most patients will die from malignant bowel obstruction, but others may pass away due to increased vulnerability to additional cancers and other comorbidities.[15,31] Age, stage at diagnosis, sub-type, and type of treatment are the most consistent and direct predictors of prognosis.[32] Along with an increased incidence of ovarian cancer among women aged 65 and older compared to younger women, there is also an increased risk of mortality.[33,34] For example, the crude probability of death for a 15–54-year-old in Canada five years after diagnosis is 31.8%, but this rises to 62.9% for someone aged 64-74 years old and 77.6% for those aged 75+.[35] This is likely explained by age associations with high histological grade and stage, frailty and comorbidities, suboptimal surgery outcomes, and patients and/or their physicians choosing to deviate from guideline concordant care.[36,34,37] Similar trends are seen with advancing stage, with 5-year survival in Canada being 90% for stage I, 70% for stage II, 39% for stage III, and 17% for stage IV.[3] This explains the poor overall survival for ovarian cancer, as over

70% of women are diagnosed at an advanced stage.[38] It is important to note, however, that there are large, unexplained international variations in survival within each stage group. For example, 5-year survival of localized disease is 95.5% in Hong Kong, but only 68.3% in Mississippi.[38] The sub-type and tumor biology of ovarian cancers can have large impacts on an individual's chances at survival. The prognosis is consistently lowest for the most common type of ovarian cancer, high-grade serous carcinomas, with overall 5-year survival being 43% compared with 82% for endometrioid carcinomas, 75% for low-grade serous carcinomas, 71% for mucinous carcinomas, and 66% for clear cell carcinomas.[11,39]

Slight improvements in incidence and mortality rates have been observed due to increased diagnostic intensity and improved treatment techniques.[40,41] These have included the development and use of PARP inhibitors, the implementation of cancer patient pathways leading to earlier diagnoses, increased use of and evidence for cytoreductive procedures, and changing attitudes towards treating older patients.[42,43,44,45,46] However, improvements are not being seen for long term survival and mostly reflect extension of progression free survival.[47] As stated by Timmermans et al, these improvements "reflect prolonged disease control rather than better chances for a cure".[40]

2.2 Current Practices in Screening, Diagnosis, and Treatment

Despite decades of research, there are no proven or effective population screening methods resulting in the early detection of ovarian cancer. In 2018, the US Preventative Services Task Force reviewed all of the existing evidence on the benefits and harms of screening for ovarian cancer in asymptomatic women. They found that previous attempts

have shown no reduction in mortality, and often result in false positives leading to unnecessary and harmful interventions.[48] As a result, along with the lack of easily identifiable early-stage symptoms, over 70% of women continue to be diagnosed with advanced stage disease worldwide.[38]

Instead, efforts to detect early-stage disease rely on improving timely access to diagnostic tests or targeted screening for symptomatic or high-risk individuals, such as transabdominal/transvaginal ultrasounds and serum biomarkers such as CA125.[49] The current standard treatment for ovarian cancer includes primary debulking surgery often followed by adjuvant platinum-based chemotherapy or neo-adjuvant chemotherapy (NACT) followed by interval debulking surgeries.[30,50,28,51] There has been contradicting evidence on which method is superior, but in any case, the goal of treatment is optimal cytoreduction to remove as much tumour as possible as those with microscopic residual disease (i.e., 0.1-10 mm of tumor) have improved survival rates.[52,53,54,55] Debulking surgery is used to not only improve the odds of survival, but also for making a diagnosis, identifying prognostic factors such as stage and histology, and reducing the effect of symptoms.[50] Treatment for recurrent disease often varies and is commonly based on the length of time between the end of primary treatment with platinum-based chemotherapy and recurrence, or the platinum-free interval (PFI).[28,29] This is because women with a short PFI have been found to respond less to re-treatment with platinum, so alternatives are often used.[29] Short PFI is also an adverse prognostic factor; those who experience a longer PFI often respond better to commonly used chemotherapies and have improved survival.[29] The guidelines and recommendations for the optimal treatment of ovarian cancer have seen little change in over a decade, despite ongoing research.

2.3 International Efforts to Understand Variations in Survival

The International Cancer Benchmarking Partnership (ICBP) is a collaboration of clinicians, policymakers, researchers, and data experts aiming to measure international variation in cancer survival.[56] The partnership is now in its second phase of comparative research, which includes 8 high income countries and 8 cancers known for having high international variation, including ovarian cancer.[56] ICBP research includes the identification and measurement of potential contributors to this variation, such as differences in age and stage distribution, diagnostic and treatment intervals and pathways, and health care system structures.

Though not specifically focused on explaining variations in survival, the CONCORD study is another international research program measuring cancer trends between countries.[57] It is the largest population-based study to look at these trends and it includes over 60 countries with a wide range of health system structures, developments, and socioeconomic status. This research has been fundamental in identifying not only how survival of ovarian cancer varies worldwide, but also in identifying differences in age, stage, and sub-type distributions. Findings from both efforts are discussed below.

2.3.1 Introduction to Factors Impacting Cancer Outcomes

There are persistent survival differences between countries for most major cancer types. The ICBP has found Australia, Canada, and Sweden to have better cancer outcomes compared to Denmark, England, Northern Ireland, and Wales.[58,59] However, these trends vary between cancer types, meaning they cannot be attributable to poorer cancer survival in general within a country.[60,61,62] For example, the ICBP SURVMARK-2 data show that while Norway has the lowest survival for colorectal cancer, it has the

highest survival for oesophageal cancer.[35]

Compared to other cancer types, ovarian cancer has seen very small gains in survival worldwide.[58] This may stem, in part, from the fact that research on other types of cancer is being done at a much higher level compared to ovarian cancer. In addition, many of the factors that have previously been found to attribute to variation in other types of cancer are not applicable to ovarian cancer. For example, variations in breast cancer survival between countries have been explained by differences in stage distribution. A study by Walters et al found that in Denmark, only 30% of breast cancer patients are diagnosed at stage I, compared to 42-45% elsewhere.[63] This may be explained by differences in access to screening tests, which do not exist for ovarian cancer. However, differences in stage distribution for ovarian cancer are minimal, and large variations in survival rates are still seen within each stage.[64,36] It has instead been hypothesized that differences in ovarian cancer survival are due to a number of individual, health system, and clinical factors independent of the disease distribution itself, such as inequalities in access to care and adherence to treatment guidelines.[58,60] Menon et al have explained that this type of variation "exists in clinical outcomes or rates of treatment that cannot be explained by disease prevalence, evidence-based care, or patient's illnesses and comorbidities".[65] These variations cost multiple lives every year and therefore identifying and understanding them should be a research priority. Although some studies have been successful in identifying possible explanations for smaller aspects of the observed variation, it remains largely unsolved.

2.3.2 Legitimate versus Illegitimate Prognostic Factors Affecting Survival

The individual, health system, and sociodemographic factors hypothesized to lead

to variations in ovarian cancer survival, from the point of diagnosis onward, can be categorized into legitimate prognostic factors and illegitimate prognostic factors. Asada et al. defines legitimate prognostic factors as those that are not amenable to policy.[66] Therefore, factors such as age at diagnosis, histological sub-type, and stage at diagnosis, can all be considered legitimate prognostic factors. In the context of this study, legitimate factors are considered those whose impact on survival can no longer be modified at the time of diagnosis. Illegitimate prognostic factors, then, are those that *are* amenable to policy intervention, and whose impact on survival can be modified at the time of diagnosis. Therefore, if negative outcomes occur as a result of these factors, it is an equity concern. This includes variation in factors like race, poverty, or continuity of care, as these can all be targeted by policy to improve access to and quality of care. It is important to note that the decision to categorize prognostic factors as legitimate or illegitimate depends on perspective, purpose, and scope. For example, stage may be considered illegitimate in some studies as it may depend on upstream factors, such as early detection. However, because the large majority of ovarian cancer cases are diagnosed at a late stage and no screening methods exist, and our focus is on equity from the point of diagnosis, at which point stage at diagnosis cannot be modified, we considered it as a legitimate prognostic factor for the purpose of this study.

2.3.3 Legitimate Prognostic Factors

Disease Characteristics

The distribution of ovarian cancer sub-types has been shown to vary between countries.[67] For example, serous subtypes have been found to make up 86.7% of India's cases, but only 16.0% of cases in the Philippines. For the endometrioid subtype, the

proportions range from 1.6% in India and 25.5% in Austria.[67] A study done in British Columbia by Dehaeck et al found that differences in sub-type distributions existed between health authority regions, with diagnoses of serous histotype ranging from 44.0%-60.7%.[68] Though it is currently unknown if this type of variation exists within Nova Scotia, this could be an important explanatory factor for variations in survival as the subtypes have considerably different survival rates.[11]

Stage at diagnosis for ovarian cancer is one of the most important prognostic factors in terms of survival.[3] With that said, the distribution of stage at diagnosis has been found to remain relatively constant both globally and within Canada.[4] In addition, there are unexplained variations in ovarian cancer survival within each stage group, with the highest 3-year survival for distant stage cancer in the ICBP being 46.9% in Australia and the lowest being 31.6% in New Zealand.[4] This is in contrast to other types of cancer, such as rectal and prostate, where variations in stage at diagnosis have been found to explain a large proportion of the observed differences in survival. A study by Yu et al found that stage at diagnosis of rectal cancer partly explained regional differences in New South Wales.[69] Similarly, a Norwegian study found that tumour stage for prostate cancer explained most of the observed regional differences in survival.[70] This trend was also identified in Finland, with the majority of regional variations in prostate survival being diminished after controlling for both age and stage distributions.[71]

There may also be variations within Canada in the proportion of women diagnosed with ovarian cancer who have mutations in the BRCA1/2 genes. That being said, we do not expect to see any significant differences in BRCA ½ gene distribution between regions throughout Nova Scotia, so this factor is unlikely to be a significant

predictor of survival differences.

Comorbidities, Frailty, and Age

A comorbidity is described as having one or more coexisting medical conditions. These are most commonly identified and measured using established indices, such as the index created by Elixhauser et al.[72] A large number of studies demonstrated the association between comorbidity and an increased risk of cancer mortality.[73] Identified mechanisms for this association include the inability to endure standard cancer treatments and increased surgical complexity/complications.[73] Though never studied within Canada, there have been mixed results on whether or not comorbidities contribute to variations in survival. A study by Noer et al found that comorbidities were not able to explain any ovarian cancer survival differences between Denmark and Sweden.[74] In contrast, a Norwegian study found that comorbidities at least partly explained regional differences in survival for multiple cancer types, though ovarian cancer was not included in the study.[70]

Frailty, which is related to comorbidity but a broader concept, is another condition usually associated with increasing age that has important impacts on cancer mortality. Frailty does not have one singular definition but has often been described as a physiologic syndrome that causes a person to be susceptible to adverse health outcomes.[75] Rules to identify frailty in an individual have been developed by Urquhart et al and include being a long-term care resident, receiving palliative care, or meeting two of seven domains identified from frailty scales, discussions with geriatricians, and health service utilization.[76] Frailty has been found to consistently increase the risk of death from multiple cancer types, including ovarian cancer.[77,78,79,80]

Age is another important prognostic factor for ovarian cancer survival, though

variations in survival as a result of variations in age distributions have never been identified. However, it is likely not increasing age itself that contributes to poorer survival, but instead its association with an increase in comorbidities and frailty. That being said, it is still an important factor to consider and control for as it is highly correlated with unmeasured frailty, senescence and disease severity.

It is important to note that in some contexts, comorbidities, and frailty may be considered illegitimate prognostic factors in that they may be a result of upstream inequities. For example, socioeconomic status has been associated with poor nutrition, alcohol use, or sustained psychosocial stressors, which all can result in the development of comorbidities or frailty.[81,82,83,84] At the time of diagnosis, however, the presence and impact of these factors can no longer be modified and therefore they are considered illegitimate within the context of this study.

2.3.4 Potentially Illegitimate Prognostic Factors

Hospital Level

Factors affecting cancer survival have been found to vary between hospitals, meaning that an individual's hospital of diagnosis and/or treatment may be a significant cause of variations in survival rates. Ovarian cancer treatment is centralized in Nova Scotia, therefore the geographic catchment area is very large. This means that most patients, who often have several months of symptoms leading to presentation, will present to a non-tertiary level hospital. As a result, there are some patients receiving treatment in hospitals that do not specialize in ovarian cancer treatment or that do not have a gynecologic oncologist on staff, which could impact their survival. There are multiple factors that may contribute to some hospitals having better survival rates than

others. For example, high ovarian cancer case volume has been shown to both directly and indirectly impact ovarian cancer outcomes by reducing failure to rescue rates (i.e., death caused by surgery complications) and increasing guideline concordant care.[50,85,86] Studies have also found that certain hospitals are less likely to provide more aggressive surgeries or any surgery at all, especially for those with advanced stage disease.[51,87,88] It is unclear why this variation exists, but it has been hypothesized that it is caused by inconsistent levels of surgical expertise across hospitals, or physicians having differing opinions on who can tolerate aggressive surgery.[88,41] For example, Norell et al found that hospitals in Norway were the least likely to avoid surgery as a result of advanced age, resulting in them having the highest survival for elderly individuals with advanced stage disease.[51] These factors are especially important within an international setting or for provinces with multiple treatment centers specializing in ovarian cancer care, but it is currently unknown if they will explain Nova Scotia's variation in survival given the high centralization of ovarian cancer care. Nova Scotia is not a large province geographically, and the province has only one tertiary hospital. That being said, not every woman will access this hospital or receive primary surgery there, so it is important to understand how this impacts survival within Nova Scotia.

Physician-Level factors

There may also be factors at the physician level that contribute to variations in survival once an individual is diagnosed. A review by Du Bois et al. found that surgery by a gynecologic oncologist results in better surgical outcomes and survival rates compared to surgery performed by a general surgeon.[89] This was especially true for those who had advanced stage disease. Similarly, a study by Urban et al in the United States

found that the lack of involvement of a gynaecologic oncologist increased the risk of an early death within 90 days after diagnosis.[90] One study conducted in Ontario found that patients who saw a gyne-oncologist instead of a general surgeon had less of a risk of undergoing repeat surgery.[91] Though this was not found to be related to survival, unnecessary repeat surgeries correspond to increased morbidity so this is likely relevant at the patient level.[91] In addition, it has been found that improved outcomes are associated with high case-volume at the surgeon level.[92] Though it is not yet known if this trend exists within Canada, research in other areas suggests that if a patient is referred to a general surgeon rather than a gyne-oncologist from their primary care provider or from the emergency department, they may have a poorer chance at survival. It has been hypothesized that the association between specialized care and better survival is a result of improved surgical staging, less time between surgery and receipt of chemotherapy, and adherence to treatment guidelines.[92, 89,91] It is currently unknown how many women in Nova Scotia who are diagnosed with ovarian cancer will never be seen by a gyne-oncologist. A study in Manitoba, however, found that 4.7% of their ovarian cancer patients had never been referred to specialist care.[93] Being seen by a gyne-oncologist prior to or following diagnosis has additional benefits outside of potentially increased survival. Cancer patients who are cared for by a specialist also receive the ability to make informed, shared decisions with their cancer care team about their preferred treatment pathways (which in some cases, may include no treatment).[94,95] In addition, accessing specialist care can lead to patients having increased access to the psychosocial resources and supports required to meet their needs during diagnosis, treatment, and follow-up care.[96,97,98] This highlights the importance of identifying if

inequities are resulting in poorer access to care.

If the first stop in the path to an ovarian cancer diagnosis is the emergency department, a patient may have a higher chance of death. This is often because those experiencing painful symptoms warranting an emergency room visit most likely have advanced stage disease.[99] In addition, routes to diagnosis through the emergency department may lead to increased surgical morbidity and in-hospital mortality.[99] Emergency department admissions for ovarian cancer are also associated with lower rates of optimal debulking surgery.[100] The mechanisms for this are unclear but it is plausible that they are due to initial surgeries being performed by general surgeons instead of gyne-oncologists, referrals to physicians who do not specialize in gynecologic oncology, or by the patient's condition making them a poor candidate for optimal cytoreduction.

One of the ways that this may be avoided is if the patient has a consistent relationship with their primary care provider. Continuity of care has been described as a physician's ongoing commitment to a patient and their family to provide well-rounded and on-going healthcare management.[101] It is used to measure the strength between the relationship of a patient and their primary care provider as a proxy for ongoing quality of care over time. High continuity of care has been associated with lower hospitalizations, fewer emergency department visits, lower mortality rates, and higher coordination with specialists.[102,103,12/15/2023 2:52:00 PM104] Though pre-diagnosis continuity of care and its association with survival has never been studied for ovarian cancer, these findings suggest that it may have an impact on survival through earlier symptom recognition, appropriate referrals to specialist care, or avoidance of emergency department visits.

Treatment Level

One of the more widely researched health system factors found to affect variations in ovarian cancer survival is adherence to treatment guidelines; although, it has not been studied within Canada. Though some guidelines for ovarian cancer differ in recommendations for treating recurrent disease and for which clinical features should trigger suspicion, they remain consistent throughout the world in terms of primary treatment.[49,51] Adherence to guidelines for ovarian cancer has been repeatedly associated with improved survival.[86,105,106,107] Despite this, there are often large and significant variations in how ovarian cancer is managed. Most commonly, clinical variations in guideline adherent care relate to decisions to undergo surgery, achieving optimal debulking, and/or receipt of appropriate chemotherapy.[105,51,92] A systematic review by White et al identified studies that have found guideline adherent care ranging from 24% in California to 78.5% in Alabama.[92] These variations in rates of adherence have been found to persist despite similar stage and comorbidity distributions.[86] The reasons for receipt of non-guideline concordant ovarian cancer care are not well understood due to a lack of research. Explanations for not achieving optimal treatment have not been consistent and it is unclear how they relate to survival; some countries attribute it to lack of hospital staffing and delays in treatment, access to high-cost drugs and clinical trials, or variations in willingness to perform surgery.[51]

Though adherence to guideline-recommended treatment has not been studied for ovarian cancer in Canada, it has been studied for breast and colorectal cancer. For breast cancer, the proportion of patients receiving appropriate treatment was highest in Ontario and lowest in Nova Scotia.[108] Receipt of treatment was associated with age, stage, comorbidities, geographic location, and income, though these associations varied

between provinces.[108] Differences in managing acute care needs during active treatment for breast cancer were also found, such as variations in the number of emergency visits versus hospitalizations.[108] Similar trends were observed for colorectal cancer. Maddison et al. found that instead of receipt of guideline concordant care being determined solely by need, it was associated with younger age, where a patient received their care, where a patient lived in the province, and the presence of comorbidities.[109] In addition, decisions on when to introduce palliative care into a patient's treatment may have an impact on survival and variations in doing so may depend on factors such as risk of severe side effects, patient choice, and perceived benefits.[110] Some studies done in lung cancer research have shown that earlier provision of palliative care (i.e. within 30 days since diagnosis) has been shown to improve the length of survival in those with advanced cancer.[111] There is a deficit of research into palliative care associations with ovarian cancer survival, however. One study was identified regarding advanced ovarian cancer, but there were no significant differences in survival between early and late introduction of palliative care.[112]

Though the link between guideline concordant care and survival appears to be clear in the literature, it can be argued that attempts to measure this association commonly ignore one important aspect: patient choice. There are many legitimate reasons why a patient and their care provider may choose to follow a different treatment pathway or avoid cancer treatment altogether. Those facing a cancer diagnosis with a poor prognosis may instead choose to live out the rest of their lives at home instead of facing treatment. A study in the Netherlands found that a significant number of ovarian cancer patients decide not to receive cancer-directed treatment, with the main reason

being patient's choice and therefore their involvement in the decision-making process.[113] This may be explained by the trade-off between quality and quantity of life. For instance, a study by Havrikesky et al found that women were willing to accept a shorter survival time if it meant avoiding the severe and distressing side-effects that come along with aggressive treatments.[114] This perspective is held not only by cancer patients; a study by Quaife et al. found that over half of respondents in the general public felt that going through cancer treatment would be worse than the cancer itself.[115] This may be true for beliefs about ovarian cancer as well, as treatments often come with several severe side effects that affect quality of life including incontinence, sexual dysfunction, lack of appetite, and diminished mobility.[116] For this reason, we have chosen to exclude guideline concordant care from our analysis and instead focus on equal access to care and patients being given the opportunity to make an informed choice with their cancer care teams.

Time Intervals

When an individual is suspected of having cancer, there are standards and guidelines for physicians to follow with respect to achieving an appropriate and timely diagnosis.[117] For example, the National Institute for Health and Care Excellence (NICE) suggests that any individual who is suspected of having cancer should be assessed within 2 weeks after being referred from primary care.[117] However, adherence to these guidelines often varies, even within areas with standardized diagnostic pathways, leading to variations in survival.[118] It is important to consider, however, that a short time to diagnosis for ovarian cancer may not equate to improved survival depending on how the patient initially presents to health care system. For example, those who present with

symptomatic, advanced stage disease will most likely have very poor survival outcomes despite the possibility for a quick diagnosis.[53] In contrast, those who arrive at their primary care physician and are diagnosed incidentally after a longer period of time may have improved survival due to less disease progression.[50] This is explained by the concept of lead time bias, where an earlier diagnosis may appear to be associated with longer survival compared to a later diagnosis. However, a diagnosis is not the same as disease onset, and individuals who are diagnosed at different points along their disease progression may not have different survival outcomes if there are no effective treatments.[119] Therefore, the association between diagnostic time intervals and survival for ovarian cancer is complicated and it is not as good an indicator for quality of care as it may be for other cancer types.

For many cancer types, research has found a similar association between survival and the time interval between diagnosis and the beginning of treatment. For example, across all stages of colorectal cancer, a longer interval between a confirmed diagnosis and the beginning of treatment is significantly associated with a higher risk of death.[120] Despite this, significant variations in meeting treatment benchmarks have been identified for colorectal patients in Nova Scotia.[109,121]Reasons for variation in achieving these benchmarks included lack of consultations with a medical oncologist, patient decision, comorbidities, socio-economic status, and advancing age.[121] Similar trends of variations in length of time to diagnosis and treatment have also been found for lung and breast cancer.[118,122] However, these associations are not as clear for ovarian cancer treatment intervals. In Nova Scotia, the diagnostic date is recorded as the date of the pathological diagnosis. That being said, it is not uncommon for neoadjuvant chemotherapy to begin

based off a cytology diagnosis prior to pathology being confirmed. In other cases, a pathological diagnosis may be made at the time of initial treatment if samples are taken during primary debulking surgery. Because of this, an "official" diagnosis date may be challenging to compute for women with ovarian cancer. Therefore, we are unable to capture the true time interval between diagnosis and treatment start date.

Socioeconomic Status

There are many additional factors, seemingly unrelated to the disease itself, that may impact an individual's outcome. For example, ovarian cancer survival has been associated with race and socio-economic status (SES). It is unclear why these associations exist and how they impact overall variations in survival, however, they point to systematic societal disparities in access to proper diagnosis and treatment pathways. As noted by Bristow et al, improvements in treatment and survival of ovarian cancer are not universal across racial and socio-economic groups.[123] Characteristics such as insurance status, household income, and education level have been shown to impact survival, with those having lower socio-economic status consistently experiencing poor ovarian cancer outcomes in comparison to more affluent groups in multiple countries.[53,123,124,125,126] These outcomes include not only poorer survival, but also an increased likelihood of being diagnosed at a late stage and receipt of non-guideline concordant care.[123, 124,125] In addition, lower SES has been associated with an increased risk of developing comorbidities and issues with self-management.[127,128] This association may not be pertinent to inequities in survival from the point of diagnosis, but it increases patient complexity and, as previously mentioned, can lead to poorer cancer survival.[127,128] Though not the focus of this particular study, this highlights the fact that improving

ovarian cancer survival may rest partly in addressing upstream inequities that result in a higher prevalence of legitimate prognostic factors. It is clear that this SES gradient is clinically relevant, as excess deaths are consistently highest in the most deprived groups for most cancer types, including colorectal, prostate, breast, and ovarian cancer.[125,129,130,131] In addition, for almost all types of cancer, increasing deprivation is associated with a higher risk of being diagnosed at an advanced stage.[132] A study by Barclay et al revealed that if the SES inequalities were removed, it would decrease the proportion of cases being diagnosed at an advanced stage by 4.1%, thereby decreasing the number of deaths.[132] Despite the Canadian Health Act aiming to enable reasonable access to health care regardless of financial or other barriers, disparities continue to persist for cancer survival.[133] These associations are strong and conclusive, but it is unknown how or if they contribute to geographical variations in ovarian cancer survival.

Race

Large and persistent ovarian cancer survival disparities have been identified for race, with black individuals consistently experiencing poorer survival rates after controlling for other disease and treatment related variables.[123,126] Though incidence rates of ovarian cancer are consistently highest in white women (85% of patients in the USA), a study by Stewart et al found that survival is up to 10% lower in black women.[11,126] This is despite similar stage distributions between each race.[126] Another study in California found that black women had a 19% increased risk for mortality, with similar findings for low socioeconomic groups.[106] These disparities are more pronounced for late-stage tumors, likely attributed to the fact that black women are less likely to undergo optimal chemotherapy and surgery when diagnosed with ovarian cancer which negatively

influences long-term survival.[47,123] It has also been hypothesized that this increased mortality may be due to unequal access to care, variations in comorbid conditions, and differences in modifiable risk factors. Similar to other patient-level factors, there has been little research to determine how race relates to geographical variations in ovarian cancer survival. It is important to understand that race is almost exclusively a social construct and not a biological variable. In addition, the black identity in Canada and Nova Scotia is made up of diverse groups and communities. Unfortunately, we were not able to include race within our analysis nor has it ever been included in population-based Canadian cancer research, because race data are not collected in Canada.

Mental Health

Multiple studies have observed an association between poor mental health and increased cancer mortality. Despite no difference in the incidence rate between those with and without mental health conditions, those suffering with mental illness have been found to be less likely to receive specialized interventions, more likely to be diagnosed at a later stage, and more likely to die from cancer-related mortality.[134,135] This is true for both pre-existing mental conditions and those developed following a cancer diagnosis. Proper treatment for mental health conditions may act as a mediator in this association, as a study by Berchuck et al found that lung cancer patients receiving proper mental health supports were more likely to receive appropriate treatment and more likely to have improved cancer outcomes in comparison to those not receiving mental health supports.[136] The association between pre-diagnosis mental health comorbidities and survival has rarely been studied for ovarian cancer and it is therefore unclear how it may contribute to variations in cancer survival. In addition, the association between mental

health and geographical variations in survival has never been studied within Canada for any cancer type.

Geography

There have been mixed findings about the association between cancer survival and where a person resides in relation to specialist care. A review by Ambroggi et al found that for multiple cancer types, longer travel requirements for treatment were associated with worse survival, advanced stage disease, a worse quality of life, and non-guideline concordant care.[137] In contrast, a study by Villanueva et al found that driving longer distances for treatment was actually associated with better ovarian cancer survival in California. They hypothesized that this is because patients were travelling longer distances to receive treatment in hospitals with a higher quality of care, rather than being treated at their local hospitals.[106] Other studies, however, have found that the distance between residence at diagnosis and the treatment center had no impact on survival.[138,139] There may also be survival differences depending on whether an individual lives in a rural or an urban area. For prostate cancer, it was found that those living in rural areas were more likely to be diagnosed with advanced stage disease compared to those in major cities.[130] An association was also found between receipt of chemotherapy and living in a rural area in Nova Scotia for early-stage breast cancer patients.[108] It is unknown if these associations exist within Nova Scotia for ovarian cancer, and due to the centralization of care, it is unclear how they would impact variations in survival.

2.4 The Mediating Effect of Equal Access to Care

It is currently unknown whether the association between ovarian cancer survival and the factors listed above are mediated by more equitable access to quality cancer care.

Though the differences in equitable access to cancer care have been well documented and described, there is a gap in the literature in terms of understanding and quantifying whether more equitable access could alleviate differences in ovarian cancer survival.[145] Most existing literature has focused on cancer types other than ovarian cancer, and often focuses on only one measure of social disparity, such as race. For example, multiple studies have been able to show that race differences in stage at diagnosis, treatment, and survival are not present in equal access health care systems, such as military hospitals.[146,147,148] Similarly, a study by Cole et al found that access-related variables explained 40% of race-based differences in survival.[149] A review of Canadian literature, on the other hand, found inequitable access to care was most often associated with income, age, and geography.[150] No research has been done to determine how or if these associations exist within ovarian cancer in Canada. This is despite of a number of studies that have illustrated the importance of equitable access to cancer care within Canadian healthcare systems.[151] In addition, the Canadian Strategy for Cancer Control has named equitable access to healthcare in the form of eliminating barriers to care as one of their top priorities, which highlights the importance of our research study.[150]

2.5 Conclusion

In conclusion, although multiple factors have been identified as determinants of ovarian cancer survival, there is very little evidence to suggest that they contribute to trends in survival variations from the point of diagnosis, or that they exist within Canada at all. This study aimed to fill this gap by determining which prognostic factors contribute to differences in ovarian cancer, and if inequities in survival and access to care exist, from point of diagnosis. In addition, we aimed to determine if regional variations in

survival exist as a result of inequal distribution of both legitimate and illegitimate prognostic variables.

Chapter 3: Objectives

The ultimate purpose of this study is to begin the process of understanding why variations in epithelial ovarian cancer survival exist, and to identify if these variations may be a result of inequities at the time of diagnosis. By analyzing potential regional differences in survival within Nova Scotia and determining which legitimate and illegitimate prognostic variables might contribute to these variations, we aimed to identify where inequities lie within the province. This helps to provide a picture of what may be occurring within other regions and provinces. To do this, we analyzed how disease, health system, and sociodemographic factors, that exist at the time of diagnosis, affect an individual's chances at survival in order to determine what puts certain groups at a higher risk of death. Specifically, we aimed to identify if inequities continued to persist once legitimate prognostic factors with a known impact on survival were taken into account. In addition, we explored whether or not legitimate or illegitimate prognostic factors are leading to inequitable access to specialist care. Many of these factors have never been studied for ovarian cancer within Canada, but they have been shown to impact variations in survival for other types of cancer within other parts of the world. The results of this research will be utilized by health care workers, researchers, and policy makers to begin paving the way to equitable access to health care and ultimately improving survival.

Objective 1

To determine which prognostic factors are contributing to potential regional variations in survival within Nova Scotia, and to identify any potential inequities associated with survival, at the point of diagnosis.

Objective 2

To assess if equitable access to health care, such as being seen by a gyne-oncologist and surgery at a tertiary hospital, impacts ovarian cancer survival at the point of diagnosis, and to determine which prognostic factors are associated with differences in access to specialist care.

2.1 To explore survival differences between those who were seen by a gyne-oncologist within 6 months prior to and following diagnosis, and those who were not, and to identify inequities associated with differences in accessing specialist care.

2.2 To explore how surgery location and surgery status (surgery at tertiary care, surgery elsewhere, or no surgery) impacts survival, and to identify inequities associated with differences in surgery location or surgery status.

Chapter 4: Methods

4.1 Data and Study Population

This study utilized a population-based retrospective design using data from multiple linked datasets. The study population included all women identified from the Nova Scotia Cancer Registry (NSCR) (ICD10 Codes) who were newly diagnosed with epithelial ovarian cancer from January 1, 2007 to December 31, 2016 (n=691). Those without a valid health card and who received primary treatment outside of Nova Scotia were excluded. Participants were censored if they were no longer eligible for Nova Scotia Medical Services Insurance (MSI) (i.e., have moved away from the province within 3 years following diagnosis).

Patient data from the NSCR were linked to a clinical database held by the Division of Gynecological Oncology at Dalhousie University (TUPPER Database) and multiple administrative health datasets held by Health Data Nova Scotia (HDNS), including MSI physician billing, CIHI Discharge Abstract Database (DAD), and the Eligibility Group Database (EGROUP). Descriptions of these data sources can be found in *Appendix A – Data Sources and Descriptions*. Data were gathered starting 3 years prior to diagnosis and ending up to 3 years post diagnosis for each patient, with the exception of the EGROUP data as these were collected if a patient had been entered into this database 5 years prior to diagnosis. The linkage of these data sources allowed us to comprehensively analyze the patient demographic, tumor, and health system factors associated with variations in ovarian cancer survival.

4.2 Variables

4.2.1 Dependent Variable

Survival Time

The main outcome for this study was the length of time a woman survived following an epithelial ovarian cancer diagnosis. The start/study entry point was the date of the diagnosis, and the event of interest/study exit point was the date of death. Both of these dates were collected from the NSCR. Those who did not pass away from ovarian cancer during the 3-year follow up period were censored at the end of the study.

4.2.2 Legitimate Prognostic Factors

For the purposes of this study, the following variables were treated as legitimate prognostic factors. As previously stated, the decision to categorize prognostic factors as legitimate or illegitimate was based on perspective, purpose, and scope. In particular, the purpose and scope of this study focused on differences in survival from the point of diagnosis.

Stage at Diagnosis

Each patient's cancer stage at diagnosis (i.e., I, II, III, IV, or unknown) was gathered from the NSCR as defined by the Collaborative Stage Data Collection System. If an individual is diagnosed with an unknown stage, it means they received limited stage work up and/or limited documentation in their health record (as defined by Cancer Care Ontario).[152] Under certain circumstances, cancer stage may be considered an illegitimate prognostic factor due to differences in access to early detection, but our focus was on factors associated with equity in survival from the point of diagnosis. In addition, almost all women will be diagnosed at a late stage due to the lack of early detection methods.

For these reasons, stage was considered a legitimate prognostic factor for the purpose of this study.

Histological Sub-Type

Based on the histology codes from the NSCR, each patient was categorized as having one of four sub-types of epithelial ovarian cancer: serous, endometroid, mucinous, or clear cell carcinoma. If additional rare sub-types exist within the dataset, they were coded as "Other". Missing histologies were coded as "unknown", as these patients did not receive a histological examination. This dataset did not allow us to differentiate between high-grade and low-grade serous histologies.

Frailty

Frailty was identified within any 365-day period within 2 years prior to an epithelial ovarian cancer diagnosis using the ICD9/10 codes from the DAD and MSI physician billing. The identification of frailty was based on decision rules described by Urquhart et al, which include being a long-term care resident, having received palliative care, or having been identified using items from the Edmonton Frailty Scale (EFS), the Clinical Frailty Scale (CFS), and/or service utilization based on the following criteria: cognitive impairment, incontinence, falls, nutrition, general health status, functional performance, or targeted health service utilization.[76] Though this measure has not been fully validated, it has been used across multiple organizations.[153,154,155] The advantage of this frailty measure is that it uses solely administrative data, which are common across jurisdictions and therefore aids in consistency and generalizability. Patients who fulfil one or more of these rules were considered frail. The variable was coded as binary (frailty/no frailty). Those with missing frailty status were coded as having no frailty, as

this means they did not meet the criteria to be considered frail.

Comorbidities

A patient's comorbidity level was calculated based on the comprehensive list of 31 comorbidities created by Elixhauser et al, excluding cancer conditions.[72] Using this list, a comorbidity count was obtained for each patient from ICD9/10 codes in the DAD up to 3 years prior to diagnosis. This comorbidity measure only captured severe comorbidities that resulted in a hospitalization or were managed during a person's hospitalization (i.e., hospital resources were used in some way to manage/treat the comorbidity during the hospitalization). These counts were then transformed into a categorical variable based on the distribution of the data and sample size within each group. The categories were labelled as 0, 1, or 2+, indicating the number of comorbidities each individual had. Those who had a missing comorbidity count were labelled as "No hospitalization", as they may have had a comorbidity without being hospitalized for it.

Age at Diagnosis

The age at diagnosis was calculated using the date of birth and date of diagnosis from the NSCR. Though it was collected as continuous, this variable was transformed into a categorical variable of <60 or 60+, based on the distribution of the data and sample size within each group.

4.2.3 Illegitimate Prognostic Factors

Mental Health

Mental health status was captured using the Canadian Chronic Disease Surveillance System. This captures any use of health services for mental illness in the DAD and MSI Physician Billing. This variable was coded as binary (mental health

comorbidity/no mental health comorbidity). Patients who visited a physician or who had been hospitalized for a mental health condition up to 3 years prior to their ovarian cancer diagnosis were coded as having a mental health comorbidity.

Poverty

Poverty acted as a proxy measure for socioeconomic status for the purpose of this study. It was identified through the Eligibility Group Database held by HDNS and defined as having been enrolled in any low-income drug program within 5 years prior to their diagnosis date. For those aged 65+, this includes being within the guaranteed income supplement category meaning they receive little to no yearly income beyond their Old Age Security pension and are therefore subject to different copay and premiums. For those below the age of 65, individuals are flagged if they are part of community services pharmacare (meaning they are on social assistance), or if they are a part of family pharmacare (meaning they have no other health insurance). We chose this measure instead of a neighbourhood level variable (such as the deprivation index), as the correlation between individual and neighbourhood income is often weak and highly conflated with geography. Instead, this variable allows us to capture an individual level measure of socioeconomic status using administrative data. Poverty was coded as a binary variable (poverty/no poverty).

Health Authority Zone at Diagnosis

The patients' health authority zone of residence at diagnosis was used to determine if regional variations in ovarian cancer survival exist. Postal codes from the time of diagnosis were collected from the NSCR and grouped into one of the four health zones (NSHA Management Zones): Central, Western, Northern, and Eastern). A map of

Nova Scotia illustrating these health zones is shown in *Appendix B - Figure 1*.

Continuity of Primary Care

A patient's continuity of care level was based on relational continuity, which is a measure of ongoing healthcare management and longitudinal quality of care. This was calculated using the Usual Provider Continuity (UPC) Index, which is the ratio of the number of times a patient visits their main primary care provider compared to the total number of times they have visited any primary care provider, within 6-30 months prior to diagnosis and excluding hospital and emergency department visits. The UPC was calculated as follows:

$$UPC = \frac{n_i}{N}$$

Where n_i = the number of patient visits with their primary care provider

And N = the number of patient visits with any primary care provider.

Though this ratio is normally a continuous measure between 0.0 and 1.0, we categorized it as high or low continuity for the purpose of this study, where a UPC of 0.75 and above was considered high continuity, and below 0.75 was considered low continuity. The number of physician visits and the physician identification number were collected through MSI physician billing (ICD-9 Codes). A UPC score could not be calculated for those who had less then 3 primary care visits overall. Therefore, these patients were included as a category titled "missing".

4.2.4 Access to Care Variables

Assessment by a Gyne-Oncologist

Patients having been assessed by a gyne-oncologist within 6 months prior to and 6 months after diagnosis was explored to determine its effect on survival, and to determine

which legitimate and illegitimate prognostic factors are associated with access to specialist care as an outcome. This was coded as a binary variable (yes/no). If a patient was identified in the TUPPER database held by the Division of Gynecological Oncology at Dalhousie within this time frame, they were coded as "yes".

Initial Surgery Location/Surgery Status

We also explored survival differences between those who received surgery at tertiary care, outside of tertiary care, or no surgery at all. Though this variable was not treated as an outcome (as many patients have legitimate reasons for choosing no surgery or different surgery locations),[113,114,115] we explored which legitimate or illegitimate prognostic factors were significantly associated with differences in this variable, in order to aid in future comparisons across provinces. This variable also acts as a proxy measure for both hospital/physician case volume as well as initial surgery being performed by a gyne-oncologist or not. The tertiary care center is described as the single hospital in Nova Scotia that provides sub-specialist care in gyne-oncology. All other hospitals were considered non-tertiary. This variable was identified through the DAD (ICD-9/10) and coded as a categorical variable (tertiary/non-tertiary/no surgery). Those who were coded as "no surgery" originally showed up within the dataset as missing. There is a chance, however, that these individuals were missing from this dataset because they had surgery outside of Nova Scotia. To determine if this was the case, we explored the other prognostic factors of this sub-population. It was found that these patients were most often older, advanced or unknown stage (likely meaning no surgery), unknown subtype (likely meaning no surgery), did not live close to the border of other provinces (meaning they likely did not go to an adjoining province for surgery), and most importantly had a much

shorter survival time. These points, along with the fact that the identified rate of no surgery matches up with no surgery rates in the literature, meant that we felt confident labelling this population as having no surgery.[156,157]

4.3 Analysis

4.3.1 Objective 1

This study began with an exploratory analysis of all of the measured prognostic factors in our data that may influence survival rates throughout Nova Scotia. All statistical analyses were completed using STATA/MP 15.1. The first step was to determine both the frequency (n) and the prevalence (%) of each patient characteristic within the population. For a prognostic factor to contribute to regional variations in survival, the prevalence of the factor itself must vary between zones. As a result, we determined if there were significant differences between each zone for each of the patient characteristics listed in 4.2. This was done using multiple chi-squared (X^2) tests with the statistical significance set to alpha level 0.05.

The next step in this objective was to determine if the outlined patient characteristics were associated with differences in survival throughout Nova Scotia, and to determine if they explained regional variations that may exist. Because the data were right censored (i.e., some deaths may have occurred after the end of the study period), models for the analysis of survival data were used. Significant associations between both the legitimate and illegitimate prognostic factors and survival were first explored using simple survival estimate techniques. Kaplan-Meier survival curves were created for significant predictor variables to visualize differences in survival estimates. Log-rank tests were then performed to determine which of these associations were statistically

significant. Although the associations between the legitimate prognostic factors and survival have already been well documented within the literature, this was still an important step as this has never been done within Nova Scotia at a population level. Not only does this provide context for the current study, but it provides a point of comparison to be used in future studies being done in other provinces, to explain variations in ovarian cancer survival throughout Canada.

Multivariable regression models were used to assess adjusted differences in survival by health zone, poverty, continuity of care, and mental illness. The purpose of this was to identify potential inequities in cancer survival, and to determine if these inequities continued to persist once we controlled for the impact that the legitimate factors had on survival at the time of diagnosis. Cox models were chosen based on the distribution of the data. A series of models were used to identify associations between illegitimate prognostic factors and survival, and to identify any regional variations in survival, by computing hazard ratios (HR), standard errors (SE) and 95% confidence intervals (CI) with the statistical significance set to alpha level = 0.05. Specifically, an HR greater than one was indicative of a higher risk of death. As previously stated, the follow-up period began at the date of diagnosis, and ended after 3 years, the date of death, or the date of the last known observation. The variables were checked for symmetry to satisfy the proportional hazards (PH) assumption. Based on conversations with the research team, some potential interactions were explored, including poverty x zone, comorbidities x frailty, and frailty x age. However, none of these interactions were significant and were therefore excluded from the reported models. As previously stated, this study was exploratory in nature, meaning the methods utilized were based on what

was found as the analysis progressed.

The method chosen to identify inequities in survival were based on methods described by Asada et al.[158] In summary, the illegitimate prognostic variables are added to regression models that have been fully adjusted for all of the legitimate prognostic variables. The purpose of this is to control for the impact of the factors known to influence survival, so that any remaining associations between the illegitimate factors and survival are therefore unexplained and are likely a result of inequities. To do this, we first ran a series of univariate regression models with both the legitimate and illegitimate prognostic factors and survival as the outcome. This was done once again to provide context for the study and provide a point of comparison for future studies. As mental illness and continuity of care were found to have insignificant associations with survival in both the descriptive statistics and univariate regression models (p-value > 0.2), these variables were not included in any multivariate models. Multivariate models were developed with zone and poverty both singly and in combination with one another, adjusted for the legitimate prognostic factors. Based on the results of these models, some supplemental descriptive statistics were generated to explore any potential explanations between the associations or lack thereof. Though not part of the main objectives of this study, this was done to enhance the discussion and improve the ability to connect our findings to the literature. Furthermore, beyond looking at statistical significance, emphasis was placed on effect sizes to discern policy-relevant disparities in survival rates.

4.3.2 Objective 2 – Part 1

For the second objective in this study, we sought to understand how access to specialist care impacts survival, and how legitimate vs. illegitimate prognostic factors are

associated with whether an individual can access this care. The variables illustrating equitable access to care included being seen by a gyne-oncologist within 6 months of diagnosis and surgery location, as described in Section 4.2.4. After testing the proportional hazards assumptions for these variables, the first step in this analysis was to determine if they were significantly associated with survival, by creating multivariate Cox models for both variables and adjusting for the factors found to have significant associations with survival in Objective 1, which therefore only included the legitimate prognostic factors.

To determine which legitimate or illegitimate prognostic factors are associated with differences in access to care, we then began to develop a logistic regression model with "being seen by a gyne-oncologist" as the outcome. First, X^2 tests were used to determine which variables were significantly associated with being seen by a gyne-oncologist prior to the regression models, and to summarize differences in these populations. Statistical significance was set to alpha level 0.05 for these X^2 tests.

Univariate logistic regression models were conducted for each legitimate and illegitimate prognostic factor, with being seen by a gyne-oncologist as the outcome variable, to once again determine which associations exist prior to and following adjustment for legitimate prognostic factors. To determine how different prognostic factors impact the chance of being seen by a gyne-oncologist, we computed odds ratios (ORs) with 95% confidence intervals and the statistical significance set to alpha level = 0.05. Specifically, an OR greater than one indicated a higher odds of being seen by a gyne-oncologist within 6 months prior to or following diagnosis. We then conducted multivariate logistic regression with the illegitimate prognostic factors of interest (i.e.,

those found to be significantly associated with the outcome), adjusted for the legitimate prognostic factors.

4.3.3 Objective 2 – Part 2

To determine how surgery location/surgery status impacts survival, we first added this variable into the same multivariate cox regression done in Objective 2 Part 1 in place of the access to a gyne-oncologist variable. In contrast to Objective 2 Part 1 we chose not to develop logistic regression models with surgery location/status as the outcome variable. This is because individuals have many legitimate reasons for choosing surgery vs. no surgery or choosing to have surgery at a different location.[113,114,115] In addition, we found that there were no significant survival differences dependent on surgery location (i.e., tertiary versus elsewhere). Therefore, these results may not be meaningful at the policy level. Instead, we used simple descriptive analysis techniques (X^2 tests) to summarize differences in these those who received surgery in different locations, and those who received surgery versus no surgery based on legitimate and illegitimate prognostic factors.

4.3.4 Ethical Approval

Ethical approval to conduct this study was granted by the Nova Scotia Health Research Ethics Board (protocol number 1027899). A waiver of consent was sought and approved, based on impracticability reasons. The data access approvals were granted by the Health Data Nova Scotia Data Access Committee and the Nova Scotia Health Privacy Office.

Chapter 5: Results

5.1 Objective 1 Results

In total, 691 individuals were identified as having been diagnosed with epithelial ovarian cancer between January 1st, 2007 and December 31st, 2016. Of these individuals, 20 were excluded as they were diagnosed via death certificate only (meaning they had a survival time of 0 days). An additional 4 individuals were excluded as they had non-epithelial ovarian cancer. This resulted in a final sample size of 667 individuals, 54% of whom survived past the follow-up period of 3 years. Around 64% of the population were diagnosed at a late stage (stage III or IV), with an additional 6.9% diagnosed with unknown stage. Of those with late or unknown stage, only 30% survived past 3 years. Most individuals had serous ovarian cancer, though over 30% had an unknown subtype. The large majority of the population were older, were not frail, and had one comorbidity. Around 40% of the population had mental illness, experienced poverty, and/or had high continuity of care. The central zone had the highest population, and the northern zone had the smallest population. These patient characteristics are shown in detail in *Table 1*.

Table 1 - Frequency and prevalence of the legitimate and illegitimate prognostic factors

Variable	Frequency (n)	Prevalence (%)
Outcome		
Survived Past 3-years		
Yes	358	53.67
No	309	46.33
Legitimate Prognostic Factors		
Stage at Diagnosis		
I	154	23.12
II	42	6.31
III	299	44.89
IV	125	18.77
Unknown	46	6.91
Histological Subtype		
Serous	286	42.88
Endometroid	37	5.55
Clear Cell	48	7.20
Mucinous	28	4.20
Other	60	9.00
Unknown	208	31.18

Variable		Frequency (n)	Prevalence (%)
Frailty			
	Frail	135	20.24
	Not Frail	532	79.76
Comorbidities			
	0	40	6.00
	1	290	43.48
	2+	224	33.58
	No Hospitalization (Missing)	113	16.94
Age at Diagnosis			
	<60	198	29.69
	60+	469	70.31
Illegitimate Prognostic Factors			
Mental Health			
	Mental Health Comorbidity	266	40.12
	No Mental Health Comorbidity	401	59.88
Poverty			
	Poverty	264	39.58
	No Poverty	403	60.42
Zone			
	Central	248	37.18
	Eastern	135	20.24
	Northern	130	19.49
	Western	154	23.09
Continuity of Care			
	High	248	41.26
	Low	353	58.74
	Missing	66	
Access to Care Variables			
Assessment by a Gyne-oncologist			
	Yes	511	76.61
	No	156	23.39
Surgery at Tertiary Care			
	Yes	365	54.72
	No	96	14.39
	No Surgery	206	30.88

n = number of individuals

For a factor to contribute to regional variations in survival, it must also vary between regions itself. As such, we conducted a series of X^2 tests between zones and each of the legitimate and illegitimate prognostic factors, the result of which are shown in Table 2. In summary, we found that comorbidity count, age, continuity of care, and poverty status differed between health zones. The eastern zone had the highest level of comorbidities, the highest number of those diagnosed above the age of 60, and the highest level of poverty. The central zone had the highest frequency of those with low continuity of care.

Table 2 - Frequency and prevalence of each patient characteristic between zones

	Zone (n (%))			
Variable	Central (n=248)	Eastern (n=135)	Northern (n=130)	Western (n=154)
Survived past 3-years				p=0.365
No	124 (50.00)	78 (57.78)	75 (57.69)	81 (52.60)
Yes	124 (50.00)	57 (42.22)	55 (42.31)	73 (47.40)
Stage				p=0.754
I	59 (23.79)	26 (19.26)	27 (20.77)	42 (27.27)
II	15 (6.05)	8 (5.93)	10 (7.69)	9 (5.84)
III	114 (45.97)	64 (47.41)	60 (46.15)	61 (39.61)
IV	46 (18.55)	26 (19.26)	20 (15.38)	33 (21.43)
Unknown	14 (5.65)	11 (8.15)	13 (10.00)	9 (5.84)
Sub-Type				p=0.463
Serous	109 (43.95)	60 (44.44)	56 (43.08)	61 (39.61)
Clear cell	25 (10.08)	5 (3.70)	6 (4.62)	12 (7.79)
Endometroid	13 (5.24)	7 (5.19)	8 (6.15)	9 (5.84)
Mucinous	11 (4.44)	5 (3.70)	5 (3.85)	7 (4.55)
Other	27 (10.89)	8 (5.93)	13 (10.00)	12 (7.79)
Unknown	63 (25.40)	50 (37.40)	42 (32.31)	53 (34.42)
Frailty				p=0.141
Frail	40 (16.13)	35 (25.93)	27 (20.77)	33 (21.43)
Not Frail	208 (83.87)	100 (74.07)	103 (79.23)	121 (78.57)
Comorbidities				p=0.039
0	13 (5.24)	8 (5.93)	7 (5.38)	12 (7.79)
1	117 (47.18)	51 (37.78)	57 (43.85)	65 (42.21)
2+	68 (27.42)	60 (44.44)	39 (30.00)	57 (37.01)
No hospitalization	50 (20.16)	16 (11.85)	27 (20.77)	20 (12.99)
Age at Diagnosis				p=0.003
<60	92 (37.10)	27 (20.00)	32 (24.62)	47 (30.52)
60+	156 (62.90)	108 (80.00)	98 (75.38)	107 (69.48)
Continuity of Care				p=0.035
Low	152 (61.29)	67 (49.63)	60 (46.15)	74 (48.05)
High	74 (29.84)	51 (37.78)	56 (43.08)	67 (43.51)
Missing	22 (8.87)	17 (12.59)	14 (10.77)	13 (8.44)
Mental Health Comorbidity				p=0.335
Yes	107 (43.15)	47 (34.81)	55 (42.31)	57 (37.01)
No	141 (56.85)	88 (65.19)	75 (57.69)	97 (62.99)
Poverty				p=0.000
Yes	65 (26.21)	76 (56.30)	53 (40.77)	70 (45.45)
No	183 (73.79)	59 (43.70)	77 (59.23)	84 (54.55)

n = number of individuals

To determine which of these factors were also significantly associated with survival differences, we conducted log-rank tests. The Kaplan-Meier curves illustrating the significant associations can be found in *Appendix B - Figure 2.* Overall, it was found that stage, sub-type, age at diagnosis, comorbidity count, frailty status, and poverty status resulted in survival differences. To get a better understanding of these associations prior to adjustment, we also developed univariate cox models with each of the illegitimate and legitimate prognostic factors and survival time as the outcome (*Table 3*). Though zone,

mental illness, and continuity of care were insignificant during the log-rank tests, we chose to continue to include them in this step of the analysis to examine the survival differences between different categories, and to see if any of the individual levels were significant.

Table 3 - Univariate Cox Regression Models

Univariate Models			
Variables	HR (SE)	95% CI	P-value
Stage (compared to stage III)			
IV	2.422 (0.298)	1.902, 3.083	0.000
II	0.180 (0.075)	0.070, 0.405	0.000
I	0.170 (0.039)	0.108, 0.267	0.000
Unknown	4.303 (0.737)	3.076, 6.019	0.000
Sub-type (compared to serous)			
Clear Cell	0.707 (0.182)	0.427, 1.170	0.177
Mucinous	0.490 (0.190)	0.229, 1.047	0.065
Endometroid	0.190 (0.097)	0.070, 0.515	0.001
Other	0.332 (0.104)	0.180, 0.614	0.000
Unknown	4.311 (0.499)	3.436, 5.409	0.000
Frailty (compared to not frail)			
Frail	4.606 (0.533)	3.671, 5.778	0.000
Comorbidity Count (compared to 1 comorbidity)			
0	1.596 (0.365)	1.019, 2.499	0.041
2+	2.318 (0.291)	1.812, 2.964	0.000
No hospitalization	2.064 (0.308)	1.540, 2.766	0.000
Age at Diagnosis (compared to <60)			
60+	3.117 (0.455)	2.342, 4.148	0.000
Continuity of Care (compared to high)			
Low	1.076 (0.122)	0.861, 1.345	0.519
Missing	1.045 (0.197)	0.722, 1.512	0.816
Mental Health Comorbidity (compared to no)			
Yes	0.994 (0.107)	0.805, 1.229	0.958
Poverty (compared to no poverty)			
Yes	1.441 (0.153)	1.170, 1.774	0.001
Zone (compared to central)			
Eastern	1.282 (0.185)	0.965, 1.701	0.086
Northern	1.263 (0.185)	0.948, 1.682	0.111
Western	1.148 (0.164)	0.867, 1.518	0.336

HR = Hazard Ratio, SE = Standard Error, CI = Confidence Interval

As expected, we found that unknown stage had the highest risk of death compared to stage III, followed by stage IV. Compared to serous sub-type, only unknown subtype had a higher risk of death. A higher risk of death was also associated with being frail, being diagnosed above the age of 60, and having 0, 2+ or no hospitalizations for comorbidities compared to one comorbidity. In terms of potential inequities as a result of illegitimate prognostic factors, only those who experienced poverty had a 1.4x higher risk

of death compared to those who did not. Mental health status and continuity of care continued to be insignificant (p>0.2). Overall, there were no significant differences in survival between zones. However, the eastern and northern zones had a slightly higher risk of death compared to the central zone, with p-values nearing significance (p=0.086 and p=0.111, respectively). Therefore, zone was still considered in the multivariate analysis.

The first multivariate cox model included zone adjusted for all of the legitimate prognostic factors (*Table 4 – Model 1*).

Table 4 - Multivariate cox regression models with illegitimate prognostic factors

	Model 1		Model 2	
Variables	HR (SE)	CI	HR (SE)	CI
Zone (compared to central)				
Eastern	1.068 (0.160)	0.797, 1.433	1.070 (0.166)	0.789, 1.450
Northern	1.183 (0.178)	0.881, 1.590	1.184 (0.180)	0.880, 1.595
Western	1.178 (0.172)	0.885, 1.568	1.179 (0.177)	0.878, 1.584
Poverty (compared to no poverty)				
Yes	-----	-----	0.996 (0.115)	0.794, 1.250
Stage (compared to stage III)				
IV	2.113 (0.271) *	1.643, 2.717	2.112 (0.271) *	1.642, 2.717
II	0.242 (0.103) *	0.106, 0.556	0.242 (0.103) *	0.106, 0.556
I	0.223 (0.055) *	0.138, 0.361	0.223 (0.055) *	0.138, 0.361
Unknown	1.527 (0.284) *	1.060, 2.200	1.528 (0.285) *	1.059, 2.203
Subtype				
Clear Cell	1.560 (0.413)	0.929, 2.621	1.561 (0.414)	0.929, 2.624
Mucinous	1.024 (0.408)	0.468, 2.238	1.025 (0.410)	0.468, 2.245
Endometroid	0.595 (0.311)	0.214, 1.658	0.595 (0.311)	0.214, 1.659
Other	0.568 (0.183)	0.302, 1.066	0.568 (0.183)	0.302, 1.066
Unknown	3.203 (0.406) *	2.402, 4.009	3.103 (0.410) *	2.401, 4.010
Frailty (compared to not frail)				
Frail	2.306 (0.308) *	1.775, 2.996	2.307 (0.310) *	1.773, 3.001
Comorbidity Count (compared to 1 comorbidity)				
0	0.738 (0.174)	0.465, 1.172	0.738 (0.175)	0.464, 1.175
2+	1.308 (0.175) *	1.007, 1.699	1.308 (0.275) *	1.006, 1.701
No Hospitalization	1.197 (0.186)	0.883, 1.625	1.198 (0.188)	0.881, 1.630
Age at Diagnosis (compared to <60)				
60 +	1.543 (0.238) *	1.141, 2.088	1.544 (0.238) *	1.141, 2.089

*Statistically significant result (p-value > 0.05)
HR = Hazard Ratio, SE = Standard Error, CI = Confidence Interval

Zone continued to show no associations with survival, as this did not change when controlling for the legitimate prognostic factors. As shown in the table, each category of zone became highly insignificant (p>0.2), and the hazard ratios became very

close to one. In this model, the hazard ratios for the legitimate prognostic factors remained very similar to the univariate analyses, though differences in survival between stages and sub-types were slightly reduced. In addition, only those with 2+ comorbidities now had a significantly different risk of death compared to those with 1 comorbidity.

Poverty's associations with survival appeared to be completely explained by legitimate prognostic factors. As shown in *Table 4 – Model 2,* once added to the multivariate model adjusted for these factors, poverty became highly insignificant (p=0.974). With this said, there is still a possibility that poverty may have an indirect impact on survival, as it may lead to an increased risk of developing legitimate prognostic factors, such as comorbidities or frailty.[127,84] To supplement these findings and explore these potential explanations further, additional descriptive statistics (X^2 tests) were done to determine which of the legitimate prognostic factors were found to be associated with differences in poverty status. This analysis is considered supplemental rather than a part of the main objective, as the associations being explored are likely relevant prior to diagnosis, and even prior to the development of ovarian cancer. The purpose is only to illustrate why the association between poverty and survival may have disappeared, and to avoid potential interpretations leading to the conclusion that poverty has no impact on ovarian cancer survival whatsoever. *Table 5* shows that indeed, all of these variables had associations with poverty. Those who experienced poverty were more often unknown stage and subtype, experienced frailty, had multiple comorbidities, and were more often diagnosed above the age of 60, compared to those who did not experience poverty.

Table 5 – Frequency and prevalence of legitimate prognostic factors based on poverty status

	Poverty Status	
Variables	No Poverty (n=403)	Poverty (n=264)
Stage		p=0.028
I	103 (25.56)	51 (19.32)
II	27 (6.70)	15 (5.68)
III	179 (44.42)	120 (45.5)
IV	75 (18.61)	50 (18.94)
Unknown	19 (4.71)	28 (10.61)
Sub-type		p=0.005
Serous	183 (45.41)	103 (39.02)
Clear Cell	33 (8.19)	15 (5.68)
Mucinous	17 (4.22)	11 (4.17)
Endometroid	24 (5.96)	13 (4.92)
Other	43 (10.67)	17 (6.44)
Unknown	103 (25.56)	105 (39.77)
Frailty		p=0.000
Yes	60 (14.89)	75 (28.41)
No	343 (85.11)	189 (71.59)
Comorbidities		p=0.001
0	23 (5.71)	17 (6.44)
1	199 (49.38)	91 (34.47)
2+	115 (28.54)	109 (41.29)
No hospitalization	66 (16.38)	47 (17.80)
Age at Diagnosis		p=0.000
60+	262 (65.01)	207 (78.41)
<60	141 (34.99)	57 (21.59)

n = number of individuals

5.2 Objective 2 Results – Part 1

Just over 75% of this cohort was assessed by a gyne-oncologist within 6 months prior to and following diagnosis (*Table 1*). To determine how this impacts survival, this variable was added to a multivariate cox regression, adjusted for the prognostic factors found to be significantly associated with survival in objective 1 (*Table 6 – Model 1*). This model predicted that those who are not seen by a gyne-oncologist within 6 months of diagnosis have a risk of death that is 2.76x higher than those who were.

Table 6 - Multivariate cox regression models with access to care variables

	Model 1		Model 2	
Variables	HR (SE)	CI	HR (SE)	CI
Seen Within 6 Months (compared to yes)				
No	2.756 (0.377) *	2.108, 3.602	-----	-----
Surgery Location (compared to tertiary care centre)				
Elsewhere	-----	-----	1.085 (0.239)	0.704, 1.670
No Surgery	-----	-----	2.647 (0.426) *	1.931, 3.628
Stage (compared to stage III)				
IV	1.880 (0.245) *	1.456, 2.427	1.805 (0.234) *	1.399, 2.328
II	0.245 (0.104) *	0.107, 0.561	0.260 (0.110) *	0.114, 0.596
I	0.209 (0.051) *	0.129, 0.337	0.237 (0.058) *	0.146, 0.384
Unknown	0.855 (0.169)	0.580. 1.262	1.284 (0.238)	0.893, 1.846
Subtype				
Clear Cell	1.422 (0.378)	0.844, 2.394	1.330 (0.353)	0.325, 1.163
Mucinous	0.964 (0.384)	0.441, 2.104	0.878 (0.352)	0.401, 1.926
Endometroid	0.557 (0.290)	0.200. 1.548	0.524 (0.274)	0.188, 1.461
Other	0.605 (0.193)	1.456, 1.131	0.615 (0.200)	0.325, 1.163
Unknown	2.576 (0.349) *	1.975, 3.360	1.284 (0.238) *	0.893, 1.846
Frailty (compared to not frail)				
Frail	2.266 (0.305) *	1.740, 2.951	1.821 (0.250) *	1.392, 2.382
Comorbidity Count (compared to 1 comorbidity)				
0	0.734 (0.172)	0.463, 1.163	0.811 (0.192)	0.510, 1.292
2+	1.215 (0.162)	0.936, 1.579	1.239 (0.166)	0.953, 1.610
No Hospitalization	1.165 (0.180)	0.860, 1.578	1.042 (0.163)	0.767, 1.417
Age at Diagnosis (compared to <60)				
60 +	1.426 (0.221) *	1.053, 1.933	1.349 (0.213)	0.990, 1.837

*Statistically significant result (p-value > 0.05)
HR = Hazard Ratio, SE = Standard Error, CI = Confidence Interval

As we wanted to determine which prognostic factors were associated with a higher or lower chance of being seen by a gyne-oncologist, we first conducted X^2 tests between this outcome and the legitimate and illegitimate prognostic factors (*Table 7*).

Table 7 - Frequency and prevalence of each patient characteristic, between those who were and were not seen by a gyne-oncologist within 6 months of diagnosis.

Seen Within Six Months of Diagnosis (n (%))		
Variables	Yes (n=511)	No (n=156)
Stage		p=0.000
I	136 (26.61)	18 (11.54)
II	<40 (<10) *	5 (3.21)
III	259 (50.86)	40 (25.64)
IV	75 (14.68)	50 (32.05)
Unknown	<4 (<1) *	43 (91.49)
Sub-type		p=0.000
Serous	262 (51.27)	24 (15.38)
Clear Cell	42 (8.22)	6 (3.85)
Mucinous	25 (4.89)	<5 (<5) *
Endometroid	33 (6.56)	<5 (<5) *
Other	56 (10.96)	<5 (<5) *
Unknown	93 (18.20)	115 (73.72)
Frailty		p=0.000
Yes	59 (11.55)	76 (48.72)
No	452 (88.45)	80 (51.28)

Variables	Yes (n=511)	No (n=156)
Comorbidities		p=0.000
0	30 (5.87)	10 (6.41)
1	248 (48.53)	42 (26.92)
2+	150 (29.35)	74 (47.44)
No hospitalization	83 (16.24)	30 (19.23)
Age at Diagnosis		p=0.000
60+	331 (64.77)	138 (88.46)
<60	180 (35.23)	18 (11.54)
Continuity of Care		p=0.896
Low	273 (53.42)	80 (51.28)
High	188 (36.79)	60 (38.42)
Missing	50 (9.78)	16 (10.26)
Mental Health Comorbidity		p=0.431
Yes	208 (40.70)	58 (37.18)
No	303 (59.30)	98 (62.82)
Poverty		p=0.000
Yes	179 (35.05)	85 (54.49)
No	332 (64.97)	71 (45.51)
Zone		p=0.000
Central	209 (40.90)	39 (25.00)
Eastern	94 (18.40)	41 (26.28)
Northern	86 (16.83)	44 (28.21)
Western	122 (23.87)	32 (20.51)

*Due to privacy policy, cell sizes less than 5 were approximated
n = number of individuals

We found that nearly every variable, with the exception of mental illness and continuity of care, had a significant association with being seen by a gyne-oncologist. Nearly 90% of all those diagnosed at stage I-III were seen within six months, compared to only 40% of those diagnosed at stage IV and 8% of those diagnosed at an unknown stage. Similar trends were seen with sub-type: the majority of those seen within 6 months of diagnosis had serous subtype, whereas the majority of those not seen within 6 months had an unknown subtype. The highest frequency of being seen within 6 months also occurred for those who were not frail, who had 1 comorbidity, who were below the age of 60, and who did not experience poverty. Regional differences were also seen with this outcome, as the highest number of individuals seen within 6 months resided in the central zone, and the lowest number of those not seen within 6 months resided in the western zone.

To develop a better understanding of these associations, both univariate and multivariate logistic regressions were conducted with being seen by a gyne-oncologist as the outcome (*Table 8)*. The univariate models were conducted for each legitimate and illegitimate prognostic factor (*Table 8 – Model 1*). The multivariate model, however, included only variables found to be significantly associated with the outcome in both the univariate models and the X^2 tests (*Table 8 – Model 2*).

Table 8 - Univariate and multivariate logistic regression models showing odds of being seen by a gyne-oncologist within 6 months of diagnosis, between prognostic factors.

	Model 1 (Univariate)		Model 2 (Multivariate)	
Variables	OR (SE)	CI	OR (SE)	CI
Stage (compared to stage III)				
IV	0.232 (0.058) *	0.142, 0.378	0.317 (0.093) *	0.178, 0.562
II	1.143 (0.578)	0.424, 3.080	0.812 (0.489)	0.249, 2.646
I	1.167 (0.353)	0.644, 2.113	0.708 (0.259)	0.345, 1.451
Unknown	0.014 (0.008) *	0.005, 0.042	0.042 (0.025) *	0.013, 0.136
Subtype (compared to serous)				
Clear Cell	0.641 (0.311)	0.247, 1.661	0.389 (0.212)	0.302, 3.352
Mucinous	0.763 (0.494)	0.215, 2.714	0.746 (0.562)	0.170, 3.264
Endometroid	0.756 (0.431)	0.247, 1.313	0.661 (0.440)	0.179, 2.439
Other	1.282 (0.718)	0.428, 3.841	1.006 (0.618)	0.302, 3.352
Unknown	0.074 (0.019) *	0.045, 0.122	0.171 (0.050) *	0.096, 0.305
Frailty (compared to not frail)				
Frail	0.137 (0.029) *	0.091, 0.208	0.422 (0.125) *	0.236, 0.756
Comorbidity Count (compared to 1 comorbidity)				
0	0.508 (0.204)	0.231, 1.116	0.815 (0.419)	0.298, 2.233
2+	0.343 (0.075) *	0.223, 0.527	0.617 (0.184)	0.344, 1.106
No Hospitalization	0.469 (0.127) *	0.276, 0.796	0.466 (0.174) *	0.224, 0.968
Age at Diagnosis (compared to <60)				
60 +	0.240 (0.064) *	0.142, 0.405	0.607 (0.203)	0.315, 1.168
Continuity of Care (compared to high)				
Low	1.089 (0.213)	0.743, 1.597	-----	-----
Missing	0.997 (0.322)	0.529, 1.879	-----	-----
Mental Health Comorbidity (compared to no)				
Yes	1.160 (0.219)	0.802, 1.678	-----	-----
Poverty (compared to no poverty)				
Yes	0.450 (0.084) *	0.313, 0.648	0.703 (0.177)	0.429, 1.151
Zone (compared to central)				
Eastern	0.428 (0.109) *	0.259, 0.706	0.512 (0.180)	0.257, 1.018
Northern	0.365 (0.093) *	0.221, 0.601	0.294 (0.099) *	0.153, 0.567
Western	0.711 (0.188)	0.424, 1.194	0.911 (0.316)	0.462, 1.780

*Statistically significant result (p-value > 0.05)
OR = Odds Ratio, SE = Standard Error, CI = Confidence Interval

Once again, the association between poverty and being seen by a gyne-oncologist was fully explained by the legitimate prognostic factors, as this association disappeared in the fully adjusted model (p=0.162). Some inequities continued to persist, however, as the

northern zone was associated with a lower odds of being seen by a gyne-oncologist compared to the central zone, in both the univariate and multivariate models. Those diagnosed at stage IV or unknown stage had a lower odds of being seen compared to those diagnosed at stage III. Similarly, only those with unknown subtype had a significantly lower chance of being seen compared to those with serous subtype. Only those who had not been hospitalized for a comorbidity had a significantly lower chance of being seen compared to those with 1 comorbidity. Frail individuals had a lower odds of being seen compared to those who were not frail. Age differences were not significant in this model.

5.3 Objective 2 Results – Part 2

Around 30% of this cohort did not have surgery for their cancer. Of those who did, 79.2% received it at the tertiary care center (*Table 1*). As was done in Objective 2 part 1, we added this variable to the multivariate cox regression, adjusted for the legitimate prognostic factors found to be associated with survival (*Table 6 – Model 2).* We found that having no surgery was associated with an increased risk of death that was 2.65x higher than those who received surgery at tertiary care. However, there were no significant differences in survival for those who received surgery at a non-tertiary care center (p=0.713). *Table 9* shows differences in prognostic factors between those who did and did not receive surgery. We found that surgery status is significantly associated with stage, sub-type, frailty, comorbidities, age at diagnosis, poverty, and being seen by a gyne-oncologist. Unsurprisingly, those who did not receive surgery were more frequently diagnosed at unknown stage or stage IV, had an unknown subtype, were frail, had 2+ comorbidities, and were diagnosed above the age of 60.

Table 9 - Frequency and prevalence of each patient characteristic, between those who had surgery and those who did not.

	Surgery Status (n (%))	
Variables	No Surgery	Had Surgery
Stage		p=0.000
I	<20 (<10) *	138 (29.93)
II	<5 (<5) *	39 (8.46)
III	71 (34.47)	228 (49.46)
IV	73 (35.44)	52 (11.28)
Unknown	43 (20.87)	4 (0.87)
Sub-type		p=0.000
Serous	30 (14.56)	256 (55.53)
Clear Cell	<5 (<5) *	44 (9.54)
Mucinous	<5 (<5) *	26 (5.64)
Endometroid	<5 (<5) *	33 (7.16)
Other	<5 (<5) *	59 (12.80)
Unknown	165 (80.10)	43 (9.33)
Frailty		p=0.000
Yes	103 (50.00)	32 (6.94)
No	103 (50.00)	429 (93.06)
Comorbidities		p=0.000
0	12 (5.83)	28 (6.07)
1	50 (24.27)	240 (52.06)
2+	97 (47.09)	127 (27.55)
No hospitalization	47 (22.82)	66 (14.32)
Age at Diagnosis		p=0.000
60+	188 (91.26)	281 (60.95)
<60	18 (8.74)	180 (39.05)
Continuity of Care		p=0.584
Low	106 (51.46)	247 (53.58)
High	82 (39.81)	166 (36.01)
Missing	18 (8.74)	48 (10.41)
Mental Health Comorbidity		p=0.589
Yes	79 (38.35)	187 (40.56)
No	127 (61.65)	274 (59.44)
Poverty		p=0.000
Yes	104 (50.49)	160 (34.71)
No	102 (49.51)	301 (65.29)
Zone		p=0.063
Central	62 (30.10)	186 (40.35)
Eastern	47 (22.82)	88 (19.09)
Northern	48 (23.30)	82 (17.79)
Western	49 (23.79)	105 (22.78)
Seen by a Gyne-Oncologist Within 6-Months		P=0.000
Yes	75 (36.41)	436 (94.58)
No	131 (63.59)	25 (5.43)

* Due to privacy policy, cell sizes less than 5 were approximated
n = number of individuals

Surprisingly, poverty was associated with differences in surgery status, as 50% of those who did not have surgery experienced poverty, compared to 35% of those who did have surgery. Zone was slightly insignificant (p=0.063), with Northern zone having the highest percentage of those who did not receive surgery, and central zone having the

lowest. Being seen by a gyne-oncologist also appeared to be an important predictor of surgery status, as 95% of people who received surgery had been seen within 6 months of diagnosis, compared to 36% of those who did not receive surgery.

Table 10 illustrates differences in prognostic factors between those who received surgery at tertiary care versus elsewhere. We found that those who received surgery elsewhere in comparison to tertiary care were more often low stage (stage I), non-serous subtype, non-frail, had 0 comorbidities, and were not seen by a gyne-oncologist within 6 months prior to or following diagnosis.

Table 10 - Frequency and prevalence of each patient characteristic, between those who had surgery at tertiary care and those who had surgery elsewhere.

	Surgery Location (n (%))	
Variables	Tertiary Care (n=365)	Elsewhere (n=96)
Stage		p=0.006
I	96 (26.30)	42 (43.75)
II	<35 (<10) *	<10 (<10) *
III	196 (53.70)	32 (33.33)
IV	40 (10.96)	12 (12.50)
Unknown	<5 (<5) *	<5 (<5) *
Sub-type		p=0.017
Serous	215 (58.90)	41 (42.17)
Clear Cell	36 (9.86)	8 (8.33)
Mucinous	18 (4.93)	8 (8.33)
Endometroid	26 (7.12)	7 (7.29)
Other	38 (10.41)	21 (21.88)
Unknown	32 (8.77)	11 (11.46)
Frailty		p=0.016
Yes	20 (5.48)	12 (12.50)
No	345 (94.52)	84 (87.50)
Comorbidities		p=0.026
0	16 (4.38)	12 (12.50)
1	191 (52.33)	49 (51.04)
2+	103 (28.11)	24 (25.00)
No hospitalization	55 (15.07)	11 (11.46)
Age at Diagnosis		p=0.126
60+	229 (62.74)	52 (54.17)
<60	136 (37.26)	44 (45.83)
Zone		p=0.702
Central	151 (41.37)	35 (36.46)
Eastern	71 (19.45)	17 (17.71)
Northern	63 (17.26)	19 (19.79)
Western	80 (21.92)	25 (26.04)
Seen by a Gyne-Oncologist Within 6-Months		p=0.000
Yes	357 (97.81)	79 (82.29)
No	8 (2.19)	17 (17.71)

	Surgery Location (n (%))	
Variables	Tertiary Care (n=365)	Elsewhere (n=96)
Continuity of Care		p=0.939
Low	197 (53.97)	50 (52.08)
High	130 (35.62)	36 (37.50)
Missing	38 (10.41)	10 (10.42)
Mental Health Comorbidity		p=0.343
Yes	144 (39.45)	43 (44.79)
No	221 (60.55)	53 (55.21)
Poverty		p=0.751
Yes	128 (35.07)	32 (33.33)
No	237 (64.93)	64 (66.67)

* Due to privacy policy, cell sizes less than 5 were approximated
n = number of individuals

Chapter 6: Discussion

A key aim of this study was to determine whether regional variations in ovarian cancer survival, from the point of diagnosis, existed throughout Nova Scotia, and if so, to explore if the legitimate or illegitimate prognostic factors might help explain these variations. While our initial investigations using log-rank tests showed very slight differences in survival time between the four NSHA management zones that divide the province, these dissolved completely in the univariate analysis. This is an encouraging finding for Nova Scotia, suggesting that where an individual lives in the province is not associated with survival time once diagnosed.

We also investigated if there were associations between individual-level prognostic factors and survival that could highlight potential equity concerns. However, we found that any existing variations in survival between illegitimate factors, which may result in inequitable access to care, were also fully explained by differences in legitimate prognostic factors. Notably, mental health and pre-diagnostic continuity of care had no discernable impacts on survival disparities. Poverty, on the other hand, showed a univariate association with survival that then disappeared once the legitimate prognostic factors were controlled. Essentially, this indicates that, at the time of diagnosis, any differences in survival attributed to poverty were explained by differences in legitimate prognostic variables. However, this does not mean that poverty has no impact on survival at all. Our supplemental analysis suggests that an association between and survival may reside within upstream associations with legitimate prognostic factors (i.e., comorbidities and/or frailty) prior to the point of diagnosis.

Another aim of this study was to explore differences in access to specialist care, and to delineate the differences between those who are seen by a gyne-oncologist and those who are not, as well as those who undergo surgery at a tertiary hospital versus elsewhere or not at all. Indeed, both of these factors resulted in substantial survival differences (with the exception of surgery at tertiary care versus surgery elsewhere). Whether or not someone was assessed by a gyne-oncologist appeared to impact the likelihood of receiving surgery, and in itself has significant impacts on survival rates. We chose to develop regression models with assessment by a gyne-oncologist as an outcome, given that the goal of the gyne-oncologists in Nova Scotia is to ensure timely consultations with every individual who has been diagnosed with ovarian cancer. Our study shows, however, that this is not the case. Just under one-quarter of this cohort was not seen within 6 months prior to or following diagnosis. In our descriptive and univariate analyses, those who had a lower chance of being seen by a gyne-oncologist were late or unknown stage, were older, had more complexities, experienced poverty, and lived in the northern or eastern zone. In our fully adjusted model, however, poverty no longer had a significant association with survival, meaning that differences in access to care are mostly related to differences in legitimate prognostic factors at the time of diagnosis. With that said, the northern zone continued to have an association with a lower chance of being seen by a gyne-oncologist, which was not explained by the legitimate prognostic factors and instead must be a result of another unmeasured factor.

Perhaps unsurprisingly, we found that when a person does not receive surgery, they have a much shorter survival time. As outlined in the methodology, we did not look into this factor as an outcome, as patient and physician decision making is a major

determinant of whether or not someone receives surgery, and this cannot be captured using administrative data. Nevertheless, we were able to identify some differences in this population that may be important in future comparative studies between provinces. On average, at the time of diagnosis, those who did not receive surgery were older, had more complexities (i.e., frailty or comorbidities), and a higher cancer stage. We also found that those who received surgery elsewhere had a lower stage and a non-serous subtype, compared to those who received surgery at tertiary care. In the descriptive analyses, we did identify some socioeconomic disparities in surgery status, which may warrant further investigation in future studies.

The lack of survival differences based on poverty status, from the time of diagnosis, was perhaps the most surprising finding. This is because the literature has consistently shown that cancer survival disparities due to socioeconomic status are clear and substantial.[159,160,161] However, it is noteworthy that the majority of research regarding this association has not specifically focused on ovarian cancer, and therefore socioeconomic disparities may not manifest in the same was as they do for other cancer types. The large majority of ovarian cancer patients are diagnosed at a very late stage, resulting in universally short survival times. In other cancer types, there are differences in the stage at diagnosis due to socioeconomic status, which can greatly impact survival.[132,162,163] With that said, it is also true that the majority of these studies did not focus specifically on how these inequities continue to persist from the point of diagnosis moving forward, and instead they often take upstream disparities into account. Therefore, it is important to recognize that our findings do not negate the presence of any associations between poverty and ovarian cancer survival. Rather, they highlight that

these associations indeed may exist upstream, rather than at the time of diagnosis. Though not the main objective of this study, our supplemental descriptive statistics showed that the frequency of legitimate prognostic factors differ between those with and without poverty. Those who experienced poverty were more often diagnosed with an unknown stage or sub-type, experienced frailty and multiple comorbidities, and were diagnosed at an older age. As these factors all have direct impacts on survival themselves, it is important to understand how poverty may increase the risk of these factors and therefore indirectly increase the risk of death. Firstly, multiple studies have demonstrated that poverty can increase the risk of developing frailty or comorbidities.[127,84] A comprehensive review by Pathirana and Jackson, which included Canadian studies, found that increased deprivation is consistently associated with an increased risk of developing comorbidities.[164] Similarly, the Women's Health and Aging Studies done in the United States found that those with low socioeconomic status had double the risk of developing frailty compared to those with high socioeconomic status.[165] These associations may be explained by the relationship between socioeconomic status and unhealthy behaviours, which may lead to the development of comorbidities and frailty. For example, multiple studies have found that smoking, alcohol use, physical inactivity, sustained psychosocial stressors, and unhealthy diets are all more prevalent in those with lower socioeconomic status.[166,81,83,82] The reason that individuals experiencing poverty were more often diagnosed at an unknown stage or sub-type is less clear. One potential explanation lies in the socioeconomic disparities impacting access to healthcare as a result of upstream associations with legitimate prognostic factors. As described in the results of the second objective, those experiencing poverty had a lower odds of being assessed by a gyne-

oncologist in the univariate model, though once again this is association was explained by upstream factors. As diagnosis and staging are most accurate when done by a gyne-oncologist, this may indirectly explain why those with poverty were most often diagnosed with an unknown stage or subtype.[167,168] Perhaps, this points to the conclusion that Nova Scotia's poor ovarian cancer survival in comparison to other Canadian provinces may stem from poorer health status overall and upstream influences on survival, driven by socioeconomic disparities. Therefore, perhaps improving survival rates within Nova Scotia lies in addressing these upstream factors.

It is difficult to make comparisons to existing literature to explain why regional variations in ovarian cancer survival do not appear to exist in Nova Scotia at the time of diagnosis due to the limited availability of relevant literature on this subject. Some studies conducted in the United States have found mixed results. For example, a study by Wang et al identified regional variations throughout the country in terms of survival and stage distribution, but this study design differed significantly from most as they compared only two regions which spanned multiple states, and therefore multiple healthcare systems.[169] Conversely, a study done in the United States by Farrow et al divided regions by states and found that no regional variations for ovarian cancer survival existed.[170] Only one Canadian study was identified that explored this topic: Dehaeck et al did identify regional variations in survival throughout British Columbia, though these vanished when adjusted for legitimate prognostic factors.[68]

For other cancer types, these associations are more consistent. For instance, a recent Canadian study identified significant differences in colorectal cancer survival across 14 health regions in Ontario.[171] The researchers found that much of this variation

was explained by "case-mix" factors, such as stage. Similarly, a study done in Norway found that regional variations in prostate and breast cancer survival were decreased when adjusting for stage differences.[70] Beyond geographical considerations, such as access to specialist care or distance from hospitals, this may reflect regional differences in access to screening programs for other cancer types which, as described in Section 2.2, do not exist for ovarian cancer.[48] In all, it is difficult to make comparisons to variations in survival in other areas due to the unique nature of Nova Scotia's healthcare system. In British Columbia, for example, although there are a similar number of health regions (5 versus 4), there are more than eight tertiary care centers throughout their province whereas Nova Scotia only has one.[68] This, along with the fact that we found no survival differences dependent on surgery location, may point to the fact that regional variations in survival do not exist because those who choose to receive treatment for their cancer are all mostly treated at the same place, and therefore all receive high quality care. Another potential explanation for the lack of regional variation is that we did not see regional variations in the distribution of the most direct predictors of prognosis, such as stage or frailty.

Our study did not uncover any associations between an increased risk of death and poor mental health at the time of diagnosis, even before illegitimate prognostic factors were taken into account. While the relationship between poor mental health and increased cancer mortality has been well documented across various cancer types, it is important to note that many of these studies do not focus on how pre-existing mental health issues continue to impact survival following diagnosis.[172,173,174] Instead, many of these studies only begin to measure mental health after diagnosis, a time when individuals often

develop anxiety or depression as a direct result of their cancer.[175,176] Of the few studies that have looked at pre-diagnosis mental health, they found that indeed, mental health conditions such as pre-diagnosis depressive symptoms were associated with an increased risk of cancer mortality.[177,178] A review done by Davis et al found that pre-diagnosis mental health associations with survival, across various cancer types, are most pronounced for those with schizophrenia.[179] Similarly, a study by Chang et al found that cancer mortality is significantly worse for those with more severe mental disorders.[180] It is important to acknowledge that our measure of mental health was quite broad and included common mental health conditions. Perhaps if our measure had been more specific to only focus on severe conditions, we may have found some significant differences in survival.

Finally, our first objective did not reveal survival differences between those with high or low pre-diagnostic continuity of care. This topic has never been studied for ovarian cancer and seldom for pre-diagnosis continuity of care, so it is difficult to make comparisons. In general, higher continuity of care is linked with reduced hospitalizations, lower mortality rates, and improved coordination with specialist care.[103,102,104] As we also did not find an association between continuity of care and access to a gyne-oncologist, perhaps this is not a relevant factor for ovarian cancer in Nova Scotia. Future research needs to be done to understand if pre-diagnosis continuity of care impacts survival rates for other cancer types, and to explore why these associations do not appear to exist for ovarian cancer.

The findings of our second objective highlight the importance of ensuring that each individual has access to specialist care near the time of diagnosis, as access to these

services has large associations with survival. This finding aligns with what has been found in previous studies, as being seen by a gyne-oncologist is consistently associated with improved survival.[90,181,182,183] Our multivariate analysis revealed that those who were least likely to be seen by a gyne-oncologist had advanced or unknown stage, an unknown subtype, and frailty, alongside some regional disparities. Prior to adjustment, our univariate analyses shows that poverty impacts an individual's odds of being seen by a specialist, which echoes what has been found in previous research.[184] However, similar to the first objective, these associations disappeared when legitimate prognostic factors were taken into account. This again reflects that although poverty may not have a direct association with access to care at the time of diagnosis, these patients may instead experience poor upstream health outcomes (such as frailty) as a result of their lower socioeconomic status, which may result in less access to specialist care. Additionally, the descriptive statistics showed that this population tended to be diagnosed above the age of 60. The reason why these individuals were not seen by a gyne-oncologist is unclear, but previous research may provide some explanations. Weeks et al found that the reason patients were not being referred to specialist care included poor provider-to-provider communication, extended surgical wait times, and a limited number of gyne-oncologists in certain areas.[185] Another study by Weeks et al. noted that rural patients were less likely to be referred to a gyne-oncologist compared to women living in urban areas, which may explain some of the regional variations we identified as many of the communities outside of the central zone in Nova Scotia are considered rural, including the northern zone.[186] This could be attributed to challenges in transportation when accessing specialist care over long distances.[137] Multiple studies have also found that elderly patients were less

likely to receive guideline concordant care, including treatment by a gyne-oncologist, compared to their younger counterparts.[187,188] This disparity persists despite the fact that elderly patients express similar preferences for treatment compared to younger patients, and age itself has not been found to be an independent risk factor for ovarian cancer mortality.[188,189] Similarly, individuals with poor health status (i.e., frailty or comorbidities) are much less likely to receive standard treatment.[190,191] This is despite a lack of evidence on whether or not this is necessary, as so often these individuals are not included in clinical trials.[192,193] Collectively, these factors suggest that inequities exist regarding receipt of specialist care. This is concerning not only due to its association with significantly reduced survival times, but also because these patients miss out on the additional support that comes hand in hand with specialist care.[96,97,98] While it is true that many patients prioritize an improved quality of life rather than an improved length of life, it is equally true that the majority of patients wish to have autonomy in making these decisions, with the guidance of their specialist.[194,195] At the time of diagnosis, ovarian cancer patients have high informational needs and want to be fully informed of their treatment options.[195,196] It may also be a concern that of those who underwent surgery, 95% were seen by a gyne-oncologist. Conversely, among those who did not undergo surgery, only 36.4% were seen by a gyne-oncologist. Given that gyne-oncologists possess the highest level of expertise regarding ovarian cancer treatment and outcomes, it is crucial that all individuals who are diagnosed have the opportunity to discuss their options with a specialist in order to make informed decisions about which option is best for them. This highlights the need for each patient to be seen by a gyne-oncologist close to the time of diagnosis, even if longer survival is not their primary goal.

Regarding surgery location, we discovered a surprising finding: patients in Nova Scotia receiving surgery at tertiary care did not have better survival than those who received surgery elsewhere. This contradicts much of the existing literature, which consistently indicates that surgery performed by a gyne-oncologist leads to improved survival outcomes due to higher levels of optimal debulking, better staging, and fewer post-operative complications.[181] With that said, it is difficult to make appropriate comparisons to other research findings due to Nova Scotia's unique health care system. The large majority of existing research has been done in the United States, where most major cities would have multiple hospitals providing tertiary-level care to ovarian cancer patients. As Nova Scotia has only one, this may explain why our findings differed. We must also consider the fact that our descriptive statistics revealed that patients who did not receive surgery at tertiary care in Nova Scotia were more often stage I, whereas those who did receive surgery at tertiary care were most often stage III. Moreover, we found a higher incidence of individuals with sub-types other than serous who underwent surgery elsewhere. Given that stage and sub-type are the most direct and influential predictors of survival, this suggests that these individuals may have had a better prognosis in general, which may explain why we did not see survival differences between these groups despite the advantages of surgery being performed by a gyne-oncologist.

As previously stated throughout this dissertation, our study, along with many others, are unable to capture patient and physician decision making within our analysis. This may be one of the most important reasons for an individual to choose not to have surgery, as many cancer patients have a preference for a better quality of life rather than length of life, and treatment can lead to significant, long-lasting side effects.[194,196, 114]

With that said, we also found that the prevalence of poverty was highest in the non-surgery group, which suggests that equity concerns may indeed be a contributing factor here. Future research should include the measurement and analysis of how patient and physician decision making factors into these associations. Qualitative research may be utilized to understand the wants and needs of patients regarding their treatment, whether or not they are choosing to access specialist care, and any barriers they may face while doing so. This would allow policy makers and healthcare providers determine if these differences in access to specialist care and surgery status exist only as a result of a trade-off between quality or length of life, or if equity concerns are indeed at play.

6.1 Strengths

There are many strengths to this study. First, it is a population-based study meaning that we captured every woman diagnosed with epithelial ovarian cancer in Nova Scotia between the years of 2007-2016. Not only does this limit the possibility for biases, but it improves the generalizability of the results to the rest of Canada and other parts of the world with similar populations.

Second, our study is strengthened by the use of reliable datasets. The linkage of multiple administrative datasets allowed us to gather a comprehensive list of patient, tumor, and health system characteristics with limited biases. Similarly, the use of the database held by the Division of Gynecological Oncology is an asset to the study. This clinical database provides a reliable and detailed picture of a patients journey through the cancer care system that we would otherwise be unable to gather through administrative data. Each gyne-oncologist is responsible for inputting their own patient data, which limits error related to data input and missing data. In addition, the dataset is regularly

reviewed by the head of the gyne-oncology department in Nova Scotia, where any missing data that is found is manually corrected.

The use of a time-to-event outcome is another strength of this study. This allowed us to avoid grouping patients into categories based on how many years they have survived (i.e., 3-year survival). Instead, we are able to capture each individual's survival time to measure associations that are more meaningful at both the patient and healthcare worker level.

Finally, this study is strengthened through the use of patient-oriented research techniques. The study is designed to fulfil the ultimate goal of identifying areas to intervene and improving patient outcomes, particularly for the subpopulations of women within Nova Scotia with poorer survival. Patient-oriented research was integrated throughout the research by working with the gyne-oncologists responsible for ovarian cancer patient care. As the results are further disseminated and interpreted, we will work with women with ovarian cancer as Patient Partners and with Ovarian Cancer Canada over the course of the study. These perspectives will improve the interpretation of our findings and ensure we better understand why certain patients face inequitable access to care and poorer survival. Gyne-oncologists will support the application of our findings to inform practice or system changes for women in Nova Scotia. These collaborations ensure that this research is done in an environment that is closely involved with policymaking to maximize the impact of the results. In addition, this strengthens the opportunities that we will have for knowledge translation of the results and ensuring they are disseminated to the appropriate audiences.

6.2 Limitations

This study is not without its limitations. Though the use of administrative databases allowed for comprehensive data collection, there were still a number of variables that we are unable to measure without the use of chart reviews or interviews. For example, administrative data do not include any information about patient choice or health care provider decision-making. For this reason, we chose to not include any treatment variables or data pertaining to guideline concordant care as there are a number of reasons why an individual and their physician may seek different treatment routes. In addition, we were unable to measure variables such as help-seeking behaviours or race, despite their significance in the literature, due to a lack of data availability. These unmeasured variables may have led to an over or under prediction of the association between illegitimate prognostic factors and risk of death. We were also unable to include certain variables that are included in the TUPPER database because it is likely that not every patient would be included (i.e., genetic testing). Patients who are never seen by a gyne-oncologist or who are never treated at tertiary care are not entered into this database.

There are also limitations in terms of the quality of information that the variables can capture, and some of the variables are rather rudimentary measures due to the use of administrative data. For example, our comorbidity score was gathered using the DAD, meaning only those who are hospitalized for their comorbidity, or whose comorbidity was somehow managed during their hospitalization (e.g., received medications for comorbidity), were included. Individuals who did not have a hospitalization in the time period of interest were shown in the dataset as having a “missing” comorbidity count, yet

these individuals may have had comorbidities that were managed outside of hospital settings. In an attempt to appropriately categorize these individuals, we included those with "missing" comorbidity counts as those with no hospitalizations. However, this category is likely a mix of those with no comorbidities and no hospitalizations. We must also consider the fact that we were unable to differentiate between high-grade and low-grade serous histologies. This is a limitation has those with low-grade serous ovarian cancer have a 5-year survival of 75%, whereas those high-grade serous ovarian cancer have a 5-year survival of only 43%.[39] However, low-grade serous is a relatively rare form of ovarian cancer, making up less than 5% of overall cases.[197] Therefore, we do not expect this limitation to significantly impact our results.

Similarly, our measure of poverty only captured those who were flagged within pharmacare as being low income, which may have led to an over or under prediction of true poverty levels within the cohort. There may be some individuals above the age of 65 who are in the guaranteed income supplement category and are considered low income, but they may not necessarily experience poverty compared to others. A specific example may be a senior who is no longer working and therefore does not have an income stream, but they have no mortgage and therefore fewer expenses than others experiencing poverty. In addition, by capturing poverty within 5 years of diagnosis rather than 3, we may have captured those who were once impoverished but may now be in a better financial position. That being said, socioeconomic status has been shown to have lasting effects on health regardless of any changes. Individuals often fluctuate in and out of poverty, meaning that if we had chosen a shorter time frame, we may exclude those who only recently were considered not impoverished or those who would re-enter poverty

shortly after diagnosis. With that said, this measure still provides a better indicator of poverty than area measures such as the deprivation index, as neighbourhood is often only weakly associated with individual income.

There may also be a limitation in terms of missing data in the continuity of care score. We were only able to capture this score for patients who have at least three primary care visits within the specified time period. This means that individuals who did not have 3 visits showed up as having a missing value. To account for this, we created a level in the categorical variable labeled "missing" to compare these individuals to the other groups and determine if there were any significant differences in the outcome. However, this was not a large issue as most women who are affected by ovarian cancer are within an age group where primary care visits are frequent, and only 66 individuals had less than 3 primary care visits in the 2.5 years before diagnosis.

As this was a population-based study, we did not have control over the sample size. Though the study was sufficiently powered overall, we were not able to stratify out models by the legitimate prognostic factors that had major impacts on survival. Doing so would have allowed us to determine if certain prognostic factors, such as stage and frailty, may be acting as effect measure modifiers. This is a possibility as the substantial impacts of these variables on survival could have obscured smaller associations. As a result, we may have discovered inequities between the different categories of these variables (ex. within different stage groups) had we been able to conduct stratified analyses.

We were also unable to capture germline or tumour genetic mutation status, as this is largely unavailable during our study period. This is important to consider as

women with BRCA1/2 are found to have better survival compared to those without, so it needs to be considered a potential confounder and results should be interpreted with this in mind.

Regarding lead time bias, this is something we are unable to control for during the analysis due to the fact that there are currently no indicators for lead-time bias in this type of dataset. As a result, it is possible that any remaining unexplained variations in survival may be due to unmeasured confounders, such as lead time bias.

There were also some limitations with the frailty variable. First, we were unable to measure different degrees of frailty (i.e., limited vs. severe). Second, we could not capture individuals who are considered "pre-frail", but do not fit within the rules of frailty identification. That being said, frailty is being included within this study as a confounding variable and therefore these limitations did not affect our study results. In addition, we are aware that some degree of the frailty that we captured may instead be caused by the symptoms of yet-to-be diagnosed cancer. Though this may appear to be a limitation, we consider it a strength as it allows us to capture and control for some of the pre-diagnosis cancer symptoms that may act as a proxy for lead-time bias, such as weight loss. Therefore, this will strengthen our adjustment. In the dataset, we also had some individuals with missing frailty status. It is likely that these individuals did not have enough contact with the healthcare system to compute the frailty measure. Therefore, we decided to categorize these individuals as having no frailty.

Similarly, as stated in section 4.2.4, there was a large fraction of individuals who had no evidence of having surgery in our dataset. However, there was no indication on whether these individuals actually had surgery outside of the province instead. With that

said, these individuals were largely found to meet the description of someone who would not receive surgery, as they mostly had unknown or advanced stage, unknown sub-type, older age at diagnosis, and a very short survival time compared to those who whose surgery status was indicated. This proportion was also similar to what was found in the literature for surgery rates.[156,157]

Finally, we had originally planned to measure regional variations in ovarian cancer survival using the 9 former health authority regions in Nova Scotia. However, due to small sample sizes, we chose to use the four current health zones instead. With that said, health care during the study period was still largely coordinated within these 9 regions, so our results may have been more meaningful at the local level if we had been able to assess variations based on 9 (versus 4) regions.

6.3 Policy Implications and Future Research

This study provides valuable insights with significant policy implications for the management of ovarian cancer patients in Nova Scotia. Firstly, though this study did not uncover survival differences related to illegitimate prognostic factors at the time of diagnosis, it is important to acknowledge that potential inequities exist prior to diagnosis. To improve survival, then, we must address the upstream determinants of health which may be influenced by socioeconomic disparities. In addition, we need to consider how these disparities may continue on throughout cancer treatment and subsequent follow-up care, meaning the social determinants of health should be considered throughout the entire cancer trajectory. This study also revealed inequities regarding access to specialist care, which directly influences survival outcomes. Ensuring that every patient is promptly seen by a specialist around the time of diagnosis regardless of age, frailty status, stage at

diagnosis, etc. is imperative. This not only enables individuals to make informed decisions about their treatment, but may also increase their survival time. Policy efforts should focus on reducing wait times for specialist consultations, increasing referrals, and ensuring timely access to expert care regardless of geographical barriers or health status. Future research should also include the investigation of other potential prognostic factors leading to disparities in survival that cannot be captured using administrative data, such as race or patient and physician decision making. Furthermore, comparative studies between Nova Scotia and other Canadian provinces are warranted to gain a comprehensive understanding of variations in ovarian cancer survival at a national level.

6.4 Conclusion

This was the first population-based study in Canada to determine which prognostic factors impact ovarian cancer survival and access to specialist care. Initially, survival differences dependent on illegitimate prognostic factors were found, but these disappeared when accounting for legitimate prognostic factors. Though accessing a gyne-oncologist within 6 months of diagnosis had discernible impacts on survival, surgery location did not. Instead, survival differences resulted from a large proportion of individuals not undergoing surgery at all. Demographic and clinical differences between these populations emerged, warranting further investigation. Future research should focus on capturing factors affecting survival that are not attainable through administrative data, such as patient and physician decision making. This may reveal key insights into variations in survival rates between Canadian provinces to inform targeted interventions and policy changes to improve outcomes for ovarian cancer patients in Nova Scotia.

6.5 Knowledge Translation

The ultimate goal of this study was to identify areas in the healthcare system to intervene and improve outcomes, particularly for those subpopulations of women within Nova Scotia with poorer survival. The close collaboration with gyne-oncologists improves the interpretation of our findings and ensures we better understand why certain individuals face barriers to gold-standard care and/or poor survival, and supports the application of our findings to inform practice or system changes for women in Nova Scotia. This allows our study results to be disseminated in an environment that works very closely with policy makers. We will continue to work closely with patient advocacy organizations such as Ovarian Cancer Canada to improve the interpretation of our findings and to ensure the results are impactful at the patient level. In addition, we will continue to work closely with the gyne-oncologists in Nova Scotia who will help support the applications of our findings, which will in turn provide us with multiple opportunities for meaningful knowledge translation. Knowledge translation efforts at the proposal stage included presentations at 2 conferences: the Canadian Conference on Ovarian Cancer Research (CCOCR) (2022) and the Maritime Health Research Summit (2022), and presentation and discussion at the Ovarian Cancer Alliance of Nova Scotia (OCEANS) research group, which includes patient partners. Future knowledge translation efforts will include communicating our results to Ovarian Cancer Canada and other stakeholders at CCOCR 2024, creation of figures and infographics to convey our results to multiple different audiences, and at least one peer-reviewed publication. We also expect this study to act as a catalyst for further research into understanding why variations in ovarian cancer survival exist outside of Nova Scotia to understand the broader picture in Canada.

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Appendix A – Data Sources and Descriptions

Database	Description	Variables (extracted or derived)
Nova Scotia Cancer Registry (NSCR)	The Nova Scotia Cancer Registry is a comprehensive database operated by the Surveillance and Epidemiology Unit at Cancer Care Nova Scotia. It captures all new cancer diagnoses and associated patient information within the province, which are reportable by law.[198]	Survival time (date of diagnosis and date of death), stage at diagnosis, histological sub-type, age at diagnosis (date of birth and date of diagnosis), health authority zone at diagnosis
MSI Physician Billing	The MSI physician billing database provides administrative records of any billable services provided from a physician to an individual. This includes procedures, visits, diagnoses, etc. (HDNS MED Data Dictionary)	Frailty, continuity of primary care, mental health
CIHI Discharge Abstract Database (DAD)	This database collects administrative, clinical, and demographic information about hospital discharges directly from acute care facilities in Nova Scotia. This includes inpatient discharges and day surgery interventions. (CIHI Discharge Abstract Database metadata)	Frailty, comorbidities, mental health, surgery location
Eligibility Group Database (EGROUP)	This database captures individual eligibility and enrollment for publicly funded programs in Nova Scotia. (HDNS ELIG Group Data Dictionary)	Poverty
TUPPER Database	This clinical database captures clinical data from the gyne-oncology program, which includes consultation/visit, disease, diagnosis, treatment, and follow-up data.	Assessment by a gyne-oncologist

Appendix B – Supplementary Figures

Figure 1 *- Map showing the 4 Nova Scotia Health Authority Management Zones (from: http://www.nshealth.ca)*

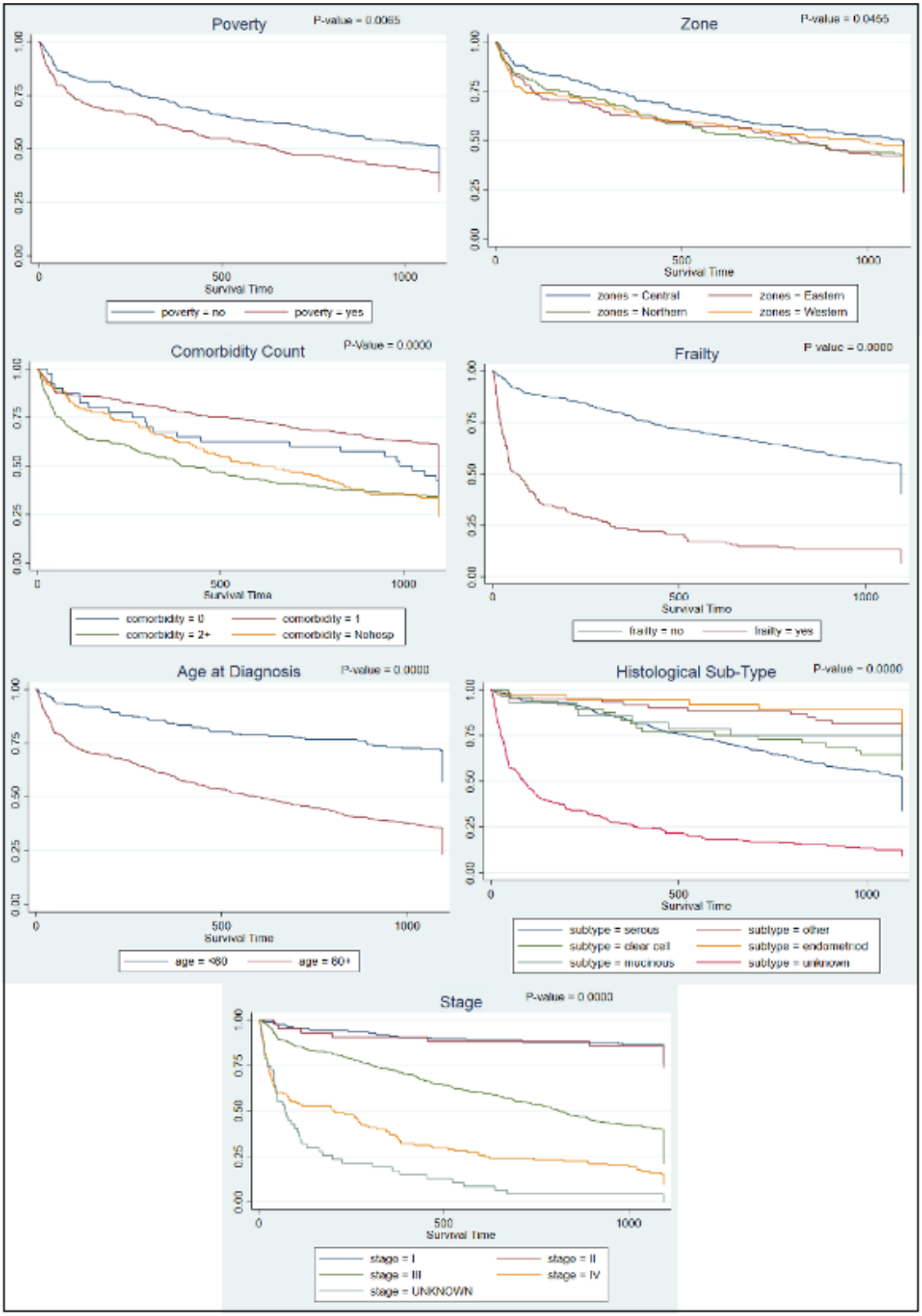

Figure 2 *- Kaplan-Meier curves & log-rank tests showing significant associations with survival.*