Retrospective Cross-Sectional Study Investigating Factors of Diagnostic and Referral Intervals for Manitoba Women with Epithelial Ovarian Cancer:

Manitoba Ovarian Cancer Outcomes (MOCO) study group

Allison J. Love[1] BSc
Pascal Lambert[2] MSc
Donna Turner[2] PhD
Robert Lotocki[3,4] MD
Erin Dean[3,4] MD
Shaundra Popowich[3,4] MD
Alon D. Altman[3,4 *] MD
Mark W. Nachtigal[3, 5, 6] PhD

1. University of Manitoba, Max Rady College of Medicine
2. Department of Epidemiology, Cancer-Care Manitoba
3. Department of Obstetrics Gynecology and Reproductive Sciences, University of Manitoba
4. Division of Gynecologic Oncology, Cancer-Care Manitoba
5. Department of Biochemistry and Medical Genetics, University of Manitoba
6. Research Institute in Oncology and Hematology, Cancer-Care Manitoba

***Corresponding author**
Alon D. Altman
RS 406, 810 Sherbrook St.
Winnipeg, MB, Canada
R3A-1R9
204-787-2967 (phone)
204-787-2314 (fax)
alon.altman@cancercare.mb.ca

Funding: This study was made possible by a CancerCare Manitoba Foundation operating grant.

Competing interests: The authors have no competing interests to disclose.

ABSTRACT

~~Objectives~~Background:

The ~~primary~~ research question~~objective~~ of this study was to examine the effects of patient demographics, comorbidities and presenting symptoms on diagnostic and referral intervals by location of first presentation (emergency room versus not). The aim is to identify factors that affect these intervals.

Methods:

Retrospective analysis of chart and medical record data for ovarian cancers, except sex cord and germ cell tumours, diagnosed between 2004 and 2010 in Manitoba, Canada. The final cohort consisted of 601 patients. Data was collected on baseline characteristics, time to diagnosis and referral, number and type of physician visits, and emergency room (ER) visits.

Results:

~~The final cohort consisted of 601 patients.~~ 63% of patients were diagnosed within 60 days of initial presentation, and 75.2% were diagnosed within 2 physician encounters. The median diagnostic interval for all stages of ER patients was 7 days, versus 55 days for non-ER patients. Non-ER early stage patients were diagnosed a median of 34.0 days later than patients with advanced disease (CI [22.22–45.69], p<0.0001). The presence of some symptoms ~~(abdominal distention and emesis)~~ was associated with shortened diagnostic intervals. ~~ER patients and those with a shorter diagnostic interval had significantly poorer survival.~~ Patients with serous ~~,carcinoma and patients with~~ clear-cell or endometrioid histotypes were less likely to have ~~suspicion~~first presentation beginning in the ER (OR=0.40, CI [0.24-0.64, p=0.0001; OR=0.28, CI [0.14-0.59], p=0.007) than those with unclassified epithelial histotype.

Interpretation:

This study has shown that the main factor associated with the diagnostic and referral intervals is presentation to the ER. These patients likely required more urgent attention for their more symptomatic ~~and potentially aggressive~~ disease, leading to quicker diagnosis and referral patterns, despite worse prognosis.

INTRODUCTION

Epithelial ovarian cancer (EOC) has the highest mortality rate of all gynecologic cancers [1-6]. The poor survival rates for EOC are frequently attributed to the fact that the majority of cases are detected at advanced stage [1-8] For EOC cases diagnosed between 2004-2007 in Alberta, Manitoba, and British Columbia, almost 65% were diagnosed at late stage with age standardized one-year relative survival of 82.3% and 57% for Stage III and IV, respectively [7]. Common thought is that to improve the prognosis of EOC, earlier detection is paramount, regardless of other characteristics [4, 9]. Delays in diagnosis and referral to a gynecologic oncologist (GynOnc) after point of suspicion are thought to contribute to poor survival overall [9].

Our objective was to measure and characterize diagnostic (time from ~~point of suspicion~~first presentation until point of diagnosis) and referral (time from ~~point of suspicion~~first presentation until encounter with GynOnc) intervals for Manitoba EOC patients by location of first presentation (emergency room versus not), and to assess the effect of variables including patient demographics, presence of comorbidities, and specific disease characteristics on the length of these time intervals.

METHODS

~~STUDY COHORT~~SETTING/DESIGN

Formatted: Font: Not Bold

Institutional research ethics board approval (HREB H2012:145) was obtained prior to developing a database encompassing EOC cases diagnosed between January 1, 2004 and December 31, 2010 for this retrospective study conducted in Manitoba, Canada. Records were identified through the Manitoba Cancer Registry (MCR). The morphologies of sex cord and germ cell were excluded.

SOURCES OF DATA

Formatted: Indent: First line: 0"

Data extracted from the MCR included histotype, grade, age at diagnosis, stage, postal code, treatment, and death date(all cause mortality). Two distinct histotype subgroups exist and are defined as: Type 1 (mucinous, low grade serous, low/moderate grade endometrioid, clear cell), and Type 2 (moderate/high grade serous, high grade endometrioid, undifferentiated, malignant mixed mesodermal tumours) [10]. Date of diagnosis was defined as the date a procedure was performed for the purposes of diagnosis (e.g. cytology, histology, blood work, imaging). Postal codes were used to identify residence at diagnosis and converted into income quintiles (stratified into urban and rural) [11]. Data extracted from patient charts included treatment, physician visits, symptoms, date of first ~~suspicion~~presentation, and type of physician. An encounter was defined as a visit with any practitioner, on an emergent or non-emergent basis. Administrative data from Manitoba Health (Physician Claims and Hospital data) were used to confirm the physician encounter date where EOC was suspected. The administrative data was also used to calculate comorbidity levels (resource utilization band) using the Johns Hopkins ACG® System (version 11.0).

Date of ~~suspicion~~ first presentation was recorded as first point of contact with any health care provider with symptoms of EOC, or where there was incidental finding of EOC. Date of referral encounter was recorded as the initial GynOnc appointment. Since this study examined medical records from hospital charts and administrative data from both physician claims and hospital admissions, we were able to identify the initial presentation for symptoms, regardless of location. Diagnostic interval was defined as the time from date of first presentation to diagnosis and the referral interval was defined as the date of first presentation to initial GynOnc visit [12, 13]. The initial form of diagnosis was also examined.

STATISTICAL ANALYSI~~E~~S

The frequency of physician and specialist encounters, from ~~suspicion~~ first presentation to diagnosis, were calculated. Quantile regression models were used to compare the time from ~~suspicion~~first presentation to diagnosis, to GynOnc encounter, and to first treatment. Predictor variables for the regression models included: age, stage, histotypes, residence, income, comorbidities, and symptoms at first presentation. Analyses were also stratified by whether first presentation was in the emergency room (ER) or not. Kaplan-Meier curves stratified by ER admission and time-to-diagnosis were also calculated. A logistic regression model was used to predict whether first presentation was ~~symptoms were first~~ reported in the ER versus elsewhere.

Analyses were conducted using R version 3.2.1. The quantreg package was used for the quantile regression models and the rms package was used for the logistic regression model. Restricted cubic splines were used for continuous predictors that violated the assumption of linearity. Other diagnostics were performed using residual and influence plots. Likelihood ratio testing was used for model building, and included testing for interactions.

RESULTS

687 patients in Manitoba were diagnosed with EOC, but 86 patients were not referred to CancerCare Manitoba ~~(CCMB)~~ and did not have chart information, leaving a final group of 601 patients. The 86 patients not referred to CancerCare Manitoba~~CCMB~~ were substantially older, had more aggressive disease, and half did not receive any treatment (data not shown). Patient demographics, disease characteristics, and symptoms at presentation stratified by location of first presentation (ER vs non-ER) are included in Table 1. The 601 EOC cases were initially diagnosed by one of several methods: histology (n = 287, 47.75%), cytology (n = 257, 42.76%), radiology (n = 42, 6.99%), serum CA-125 level (with clinical correlation) (n = 14, 2.33%). Subsequent diagnostic confirmation by histology was seen in an additional 182 cases, yielding

469 patients (78.04%) overall with diagnosis confirmed on histology, the remaining patients were not confirmed by final histology, and were treated based on cytology alone.

When the number of encounters was examined, 23.0%, 52.3%, 19.6%, 4.5%, 0.7% of EOC patients were diagnosed in 1, 2, 3, 4, and 5 encounters, respectively. Among the most frequent pathways to diagnosis, 22.0% of EOC patients had encountered a family physician and a Gynecologic Oncologist (GynOnc), 12.5% had one ER encounter, 9.3%, had an ER encounter followed by a GynOnc referral, ~~and~~ 7.2% had encountered only a family physician prior to diagnosis, and 21% had an interaction with an Obstetrician/Gynecologist during their diagnostic interval. In the cases with 2 encounters, usually a family or emergency physician referred the patient to a GynOnc. In the cases with 1 encounter, typically a family or emergency physician diagnosed the patient prior to confirmation of diagnosis by a GynOnc. Half of the cohort was seen by a GynOnc prior to diagnosis (53.6%), and only 4.66% were never seen by a GynOnc.

Almost half of the study cohort was diagnosed within 30 days of ~~suspicion~~first presentation (43.3% of all patients), and 62.6% were diagnosed within 60 days of ~~suspicion~~first presentation (Figure 1). 74% of all patients had been diagnosed within 90 days of presentation with signs or symptoms of EOC, or after incidental finding on physical exam or imaging. Due to the expected difference in diagnostic interval in the ER versus non-ER setting, analyses for diagnostic, referral, and treatment intervals were stratified by ER status at first presentation. Significant differences in diagnostic, referral, and treatment intervals were seen between ER and non-ER patients. The median diagnostic interval for an ER patient was 7 days versus 55 days for non-ER patients (Figure 1; $p<0.0001$). The median referral interval for ER patients was 18 days, whereas it was 56 days for non-ER patients (Figure 2; $p=0.0063$). Time from ~~suspicion~~first presentation to first treatment was very highly correlated with time from ~~suspicion~~first presentation to

diagnosis ($r > 0.95$; Supplemental Figure 1). Therefore, the treatment interval as an outcome was not investigated further.

To extend our analyses, we evaluated the ER and non-ER populations further to identify predictors related to diagnostic and referral intervals (Tables 2 and 3, respectively). However, most predictors as outlined in Table 1 were not statistically significant after multivariable analysis.

Survival was assessed to determine the impact of ER status and diagnostic interval (Figure 3). ER patients and patients with shorter diagnostic interval had significantly poorer survival. Predictors of ER presentation were also assessed (Table 4). The odds of a patient who presented in the ER having unclassified disease were also higher than that for a non-ER patient. Additionally, patients with high/very high comorbidities and patients with abdominal pain were more likely to first present in the ER (OR=3.028, CI[1.73-5.29], p=0.0001; OR=4.149, CI[2.44-7.07], p<0.0001, respectively), with a significant interaction between the two factors (OR=0.396, CI[0.17-0.91], p=0.0284) indicating that the effect of abdominal pain decreased if the patient had high/very high comorbidities. ~~Additionally, the odds were twice as large for patients who presented to the ER to have high/very high levels of comorbidities than moderate/lower comorbidities (OR=1.998, CI [1.33-3.01], *p*=0.0009).~~ Urban residents were more likely to present at the ER than rural patients (OR=2.421, CI[1.60-3.67], p<0.0001~~OR=2.383, CI [1.57-3.61], *p*<0.0001~~).

INTERPRETATION

The majority of EOC cases in Manitoba from 2004-2010 were diagnosed within 2 encounters and 60 days of initial presentation. Amongst non-ER patients, presentation at earlier stage and without substantial comorbidities was associated with longer diagnostic intervals. Therefore, relatively healthy patients who present with less severe symptoms likely have less urgent investigations. EOC patients who presented to the ER were more likely to have more severe disease, more often demonstrated abdominal and respiratory symptoms, and likely prompted more aggressive investigations, with led to shorter diagnostic and referral intervals. The diagnostic intervals were shorter than referral intervals, which is a reflection of other physicians diagnosing EOC before referral to subspecialists. These factors likely explain why EOC patients who presented to the ER had worse survival than those who presented elsewhere.

Our data shows that the majority of cases are diagnosed within 60 days after 2 health care encounters of ~~suspicion~~first presentation; only 5.16% of cases had 4 or more physician encounters before diagnosis.

Formatted: Indent: First line: 0"

One survey study found a median interval of 37 days from symptom onset to diagnosis [14], which is comparable to the results reported herein. Theoretically, faster diagnosis in the primary care setting would lead to earlier stage detection; however, the present study also found that first presentation in the ER and having shorter diagnostic interval are related to poorer survival. Similarly, in a study examining a cohort of adolescents and young adults with cancer, Xu *et al.* identified that having a first contact through an ER admission was related to lower survival, but that delays in the diagnostic interval or delay in treatment were not related to outcome [15]. Moreover, data from Nagle *et al.* suggests that a longer diagnostic interval for symptomatic women with invasive EOC does not adversely affect survival [16] and Robinson et al. (2012) found that increased pain scores was associated with worsened survival [17]; both studies were based on patient questionnaires and therefore open to recall bias~~.~~ Kirwan *et al.*

showed how EOC survival was related to patient age and stage at diagnosis, but that delays in patient reporting and referral from primary care was not related to survival [18]. This was also supported by Menczer et al. (2009 & 2000) who found that duration of symptoms was not associated with prognostic factors [19, 20]. Our study supports the notion that a delay in diagnosis does not contribute to poorer outcomes, and found that the main factor affecting diagnostic and referral intervals, was presentation to the ER.

Multiple studies have examined screening and early detection showing that there is no benefit to overall survival. Gilbert *et al.* trialed open access CA-125 and ultrasound testing for women with symptoms of EOC. The late stage cases detected had smaller, more resectable tumour volumes, with a larger proportion showing disease localized to the fallopian tube instead of having ovary involvement [21]. Findings from this study emphasize the need to detect disease at more resectable, lower volumes [21]. A 2010 publication showed that advanced cases of serous carcinoma (Type 2) had a shorter duration of symptoms compared to mucinous carcinoma (Type 1) [22]. This suggests that the late-stage diagnosis of serous carcinoma cases is likely due to rapid progression rather than delay in detection. One study found a mean 90.3 day interval from symptom onset to diagnosis [14], which is comparable to the results reported herein. Our study supports the previous literature showing that most patients are diagnosed within 90 days of presentation and that the diagnostic, referral, and treatment intervals are all closely related.

A strength of this study is the length of timelines of the patient journey were estimated from a combination of provincial physician billing data, hospital administration data and patient records, allowing us to use a combination "audit/database analysis" as described in Weller et al. (2012). These timelines were not based on questionnaires, thus avoided attempting to avoid patient recall bias [13]. We also examined diagnostic interval, referral interval and treatment interval and found that they were all highly correlated. One limitation of this study is that some

analyses might have been underpowered, especially in calculating the effect of variables within the smaller ER patient population. Also, all relevant information may not have been recorded in the patient charts (e.g. all symptoms at all visits). Although avoiding recall bias using this method, gathering date of first presentation from patient records may not represent the "true" initial start of patient symptoms; the patient may also have presented to the health care system with other "charted" conditions, yet still suffered from the symptoms under question. It is unknown how long the patient had symptoms prior to initial presentation, however according to Tokuda et al. (2009) ovarian cancer has a symptom interval median of 15 days and mean of 38.5 days [23].

Our study has identified that the main factor associated with the diagnostic interval in EOC cases is the setting of the initial presentation (ER vs. non-ER). Patients who presented to the ER more likely had abdominal pain and respiratory symptoms, and possibly more aggressive disease. They were likely more rapidly investigated, leading to quicker diagnosis and referral, despite poorer prognosis. By contrast, those women presenting in the community with non-specific symptoms more often had considerably longer diagnostic and referral intervals, but better outcomes.

Although it is important to emphasize EOC awareness and early detection by primary care practitioners in the community, improving the prognosis of EOC is a complex, evolving algorithm. One factor for EOC detection to be considered is the availability of primary care providers. In our cohort, it is possible that ER patients were less likely to have a regular family physician to whom they could present with symptoms, or for regular examinations. It would be useful to know the proportion of ER patients without a regular primary care provider and if there is an association with disease outcomes. The MOCO study group is further investigating

Formatted: Indent: First line: 0"

treatment algorithms, primary care availability, and adjuvant therapies to determine effects on EOC patient outcomes.

ACKNOWLEDGEMENTS

The authors acknowledge the entire team at the Manitoba Cancer Registry and CancerCare Manitoba for their administrative support and hard work, especially Gail Noonan, Mary Natividad, Katie Galloway, Sara Gray, Lori Ann Love, Danielle Chalmers, and Grace Musto. AJL completed part of this research as a component of her B.Sc. Med thesis project under the supervision of ADA and MWN. This study was made possible by a CancerCare Manitoba Foundation operating grant to ADA, DT, and MWN. The results and conclusions are those of the authors and no official endorsement by Manitoba Health, Healthy Living and Seniors is intended or should be inferred.

REFERENCES

1. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in australia, canada, denmark, norway, sweden, and the UK, 1995-2007 (the international cancer benchmarking partnership): An analysis of population-based cancer registry data. Lancet. 2011 Jan 8;377(9760):127-38.

2. Canadian Cancer Society. Canadian cancer Society's advisory committee on cancer statistics. canadian cancer statistics 2015. Annual statistics report. Toronto: Canadian Cancer Society; 2015.

3. Department of Epidemiology and Cancer Registry. Cancer in manitoba, 2012 annual statistical report. Annual report. Manitoba: CancerCare Manitoba; 2012.

4. Heintz AP, Odicino F, Maisonneuve P, Beller U, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. Int J Gynaecol Obstet. 2003 Oct;83 Suppl 1:135-66.

5. Neville F. Hacker, MD, Joseph C. Gambone, DO and Calvin J. Hobel M. Ovarian cancer . In: Merrit J AC, editor. Essentials of Obstetrics and Gynecology. 5th ed. 5th ed. Philadelphia: Saunders Elsevier Inc.; 2010. p. 412.

6. Sorensen RD, Schnack TH, Karlsen MA, Hogdall CK. Serous ovarian, fallopian tube and primary peritoneal cancers: A common disease or separate entities - a systematic review. Gynecol Oncol. 2015 Mar;136(3):571-81.

7. Maringe C, Walters S, Butler J, Coleman MP, Hacker N, Hanna L, et al. Stage at diagnosis and ovarian cancer survival: Evidence from the international cancer benchmarking partnership. Gynecol Oncol. 2012 Oct;127(1):75-82.

8. Neal RD, Allgar VL, Ali N, Leese B, Heywood P, Proctor G, et al. Stage, survival and delays

in lung, colorectal, prostate and ovarian cancer: Comparison between diagnostic routes. Br J Gen Pract. 2007 Mar;57(536):212-9.

9. Wikborn C, Pettersson F, Moberg PJ. Delay in diagnosis of epithelial ovarian cancer. Int J Gynaecol Obstet. 1996 Mar;52(3):263-7.

10. Lim A, Mesher D, Gentry-Maharaj A, Balogun N, Widschwendter M, Jacobs I, et al. Time to diagnosis of type I or II invasive epithelial ovarian cancers: A multicentre observational study using patient questionnaire and primary care records. BJOG. 2016 May;123(6):1012-20.

11. Brownell M, Mayer T, Martens PJ, Kozyrskyj A, Fergusson P, Bodnarchuk J, et al. Using a population-based health information system to study child health. Can J Public Health. 2002 Nov-Dec;93 Suppl 2:S9-14.

12. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? systematic review. Br J Cancer. 2015 Mar 31;112 Suppl 1:S92-107.

13. Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, et al. The aarhus statement: Improving design and reporting of studies on early cancer diagnosis. Br J Cancer. 2012 Mar 27;106(7):1262-7.

14. Allgar VL, Neal RD. Delays in the diagnosis of six cancers: Analysis of data from the national survey of NHS patients: Cancer. Br J Cancer. 2005 Jun 6;92(11):1959-70.

15. Xu Y, Stavrides-Eid M, Baig A, Cardoso M, Rho YS, Shams WM, et al. Quantifying treatment delays in adolescents and young adults with cancer at McGill university. Curr Oncol. 2015 Dec;22(6):e470-7.

16. Nagle CM, Francis JE, Nelson AE, Zorbas H, Luxford K, de Fazio A, et al. Reducing time to diagnosis does not improve outcomes for women with symptomatic ovarian cancer: A report from the australian ovarian cancer study group. J Clin Oncol. 2011 Jun 1;29(16):2253-8.

17. Robinson KM, Christensen KB, Ottesen B, Krasnik A. Diagnostic delay, quality of life and patient satisfaction among women diagnosed with endometrial or ovarian cancer: A nationwide danish study. Qual Life Res. 2012 Nov;21(9):1519-25.

18. Kirwan JM, Tincello DG, Herod JJ, Frost O, Kingston RE. Effect of delays in primary care referral on survival of women with epithelial ovarian cancer: Retrospective audit. BMJ. 2002 Jan 19;324(7330):148-51.

19. Menczer J. Diagnosis and treatment delay in gynecological malignancies. does it affect outcome? Int J Gynecol Cancer. 2000 Mar;10(2):89-94.

20. Menczer J, Chetrit A, Sadetzki S, National Israel Ovarian Cancer Group. The effect of symptom duration in epithelial ovarian cancer on prognostic factors. Arch Gynecol Obstet. 2009 Jun;279(6):797-801.

21. Gilbert L, Basso O, Sampalis J, Karp I, Martins C, Feng J, et al. Assessment of symptomatic women for early diagnosis of ovarian cancer: Results from the prospective DOvE pilot project. Lancet Oncol. 2012 Mar;13(3):285-91.

22. Lurie G, Wilkens LR, Thompson PJ, Matsuno RK, Carney ME, Goodman MT. Symptom presentation in invasive ovarian carcinoma by tumor histological type and grade in a multiethnic population: A case analysis. Gynecol Oncol. 2010 Nov;119(2):278-84.

23. Tokuda Y, Chinen K, Obara H, Joishy SK. Intervals between symptom onset and clinical presentation in cancer patients. Intern Med. 2009;48(11):899-905.

Retrospective Cross-Sectional Study Investigating Factors of Diagnostic and Referral Intervals for Manitoba Women with Epithelial Ovarian Cancer:

Manitoba Ovarian Cancer Outcomes (MOCO) study group

Allison J. Love[1] BSc
Pascal Lambert[2] MSc
Donna Turner[2] PhD
Robert Lotocki[3,4] MD
Erin Dean[3,4] MD
Shaundra Popowich[3,4] MD
Alon D. Altman[3,4 *] MD
Mark W. Nachtigal[3, 5, 6] PhD

1. University of Manitoba, Max Rady College of Medicine
2. Department of Epidemiology, CancerCare Manitoba
3. Department of Obstetrics Gynecology and Reproductive Sciences, University of Manitoba
4. Division of Gynecologic Oncology, CancerCare Manitoba
5. Department of Biochemistry and Medical Genetics, University of Manitoba
6. Research Institute in Oncology and Hematology, CancerCare Manitoba

***Corresponding author**
Alon D. Altman
RS 406, 810 Sherbrook St.
Winnipeg, MB, Canada
R3A-1R9
204-787-2967 (phone)
204-787-2314 (fax)
alon.altman@cancercare.mb.ca

Funding: This study was made possible by a CancerCare Manitoba Foundation operating grant.

Competing interests: The authors have no competing interests to disclose.

ABSTRACT

Background:

The research question of this study was to examine the effects of patient demographics, comorbidities and presenting symptoms on diagnostic and referral intervals by location of first presentation (emergency room versus not). The aim is to identify factors that affect these intervals.

Methods:

Retrospective analysis of chart and medical record data for ovarian cancers, except sex cord and germ cell tumours, diagnosed between 2004 and 2010 in Manitoba, Canada. The final cohort consisted of 601 patients. Data was collected on baseline characteristics, time to diagnosis and referral, number and type of physician visits, and emergency room (ER) visits.

Results:

63% of patients were diagnosed within 60 days of initial presentation, and 75.2% were diagnosed within 2 physician encounters. The median diagnostic interval for all stages of ER patients was 7 days, versus 55 days for non-ER patients. Non-ER early stage patients were diagnosed a median of 34.0 days later than patients with advanced disease (CI [22.22–45.69], $p<0.0001$). The presence of some symptoms was associated with shortened diagnostic intervals. Patients with serous ,clear-cell or endometrioid histotypes were less likely to have first presentation beginning in the ER (OR=0.40, CI [0.24-0.64, p=0.0001; OR=0.28, CI [0.14-0.59], p=0.007) than those with unclassified epithelial histotype.

Interpretation:

This study has shown that the main factor associated with the diagnostic and referral intervals is presentation to the ER. These patients likely required more urgent attention for their more symptomatic disease, leading to quicker diagnosis and referral patterns, despite worse prognosis.

INTRODUCTION

Epithelial ovarian cancer (EOC) has the highest mortality rate of all gynecologic cancers [1-6]. The poor survival rates for EOC are frequently attributed to the fact that the majority of cases are detected at advanced stage [1-8] For EOC cases diagnosed between 2004-2007 in Alberta, Manitoba, and British Columbia, almost 65% were diagnosed at late stage with age standardized one-year relative survival of 82.3% and 57% for Stage III and IV, respectively [7]. Common thought is that to improve the prognosis of EOC, earlier detection is paramount, regardless of other characteristics [4, 9]. Delays in diagnosis and referral to a gynecologic oncologist (GynOnc) after point of suspicion are thought to contribute to poor survival overall [9].

Our objective was to measure and characterize diagnostic (time from first presentation until point of diagnosis) and referral (time from first presentation until encounter with GynOnc) intervals for Manitoba EOC patients by location of first presentation (emergency room versus not), and to assess the effect of variables including patient demographics, presence of comorbidities, and specific disease characteristics on the length of these time intervals.

METHODS

SETTING/DESIGN

Institutional research ethics board approval (HREB H2012:145) was obtained prior to developing a database encompassing EOC cases diagnosed between January 1, 2004 and December 31, 2010 for this retrospective study conducted in Manitoba, Canada. Records were identified through the Manitoba Cancer Registry (MCR). The morphologies of sex cord and germ cell were excluded.

SOURCES OF DATA

Data extracted from the MCR included histotype, grade, age at diagnosis, stage, postal code, treatment, and death date(all cause mortality). Two distinct histotype subgroups exist and are defined as: Type 1 (mucinous, low grade serous, low/moderate grade endometrioid, clear cell), and Type 2 (moderate/high grade serous, high grade endometrioid, undifferentiated, malignant mixed mesodermal tumours) [10]. Date of diagnosis was defined as the date a procedure was performed for the purposes of diagnosis (e.g. cytology, histology, blood work, imaging). Postal codes were used to identify residence at diagnosis and converted into income quintiles (stratified into urban and rural) [11]. Data extracted from patient charts included treatment, physician visits, symptoms, date of first presentation, and type of physician. An encounter was defined as a visit with any practitioner, on an emergent or non-emergent basis. Administrative data from Manitoba Health (Physician Claims and Hospital data) were used to confirm the physician encounter date where EOC was suspected. The administrative data was also used to calculate comorbidity levels (resource utilization band) using the Johns Hopkins ACG® System (version 11.0).

Date of first presentation was recorded as first point of contact with any health care provider with symptoms of EOC, or where there was incidental finding of EOC. Date of referral encounter was recorded as the initial GynOnc appointment. Since this study examined medical records from hospital charts and administrative data from both physician claims and hospital admissions, we were able to identify the initial presentation for symptoms, regardless of location. Diagnostic interval was defined as the time from date of first presentation to diagnosis and the referral interval was defined as the date of first presentation to initial GynOnc visit [12, 13]. The initial form of diagnosis was also examined.

STATISTICAL ANALYSIS

The frequency of physician and specialist encounters, from first presentation to diagnosis, were calculated. Quantile regression models were used to compare the time from first presentation to diagnosis, to GynOnc encounter, and to first treatment. Predictor variables for the regression models included: age, stage, histotypes, residence, income, comorbidities, and symptoms at first presentation. Analyses were also stratified by whether first presentation was in the emergency room (ER) or not. Kaplan-Meier curves stratified by ER admission and time-to-diagnosis were also calculated. A logistic regression model was used to predict whether first presentation was in the ER versus elsewhere.

Analyses were conducted using R version 3.2.1. The quantreg package was used for the quantile regression models and the rms package was used for the logistic regression model. Restricted cubic splines were used for continuous predictors that violated the assumption of linearity. Other diagnostics were performed using residual and influence plots. Likelihood ratio testing was used for model building, and included testing for interactions.

RESULTS

687 patients in Manitoba were diagnosed with EOC, but 86 patients were not referred to CancerCare Manitoba and did not have chart information, leaving a final group of 601 patients. The 86 patients not referred to CancerCare Manitoba were substantially older, had more aggressive disease, and half did not receive any treatment (data not shown). Patient demographics, disease characteristics, and symptoms at presentation stratified by location of first presentation are included in Table 1. The 601 EOC cases were initially diagnosed by one of several methods: histology (n = 287, 47.75%), cytology (n = 257, 42.76%), radiology (n = 42, 6.99%), serum CA-125 level (with clinical correlation) (n = 14, 2.33%). Subsequent diagnostic confirmation by histology was seen in an additional 182 cases, yielding 469 patients (78.04%)

overall with diagnosis confirmed on histology, the remaining patients were not confirmed by final histology, and were treated based on cytology alone.

When the number of encounters was examined, 23.0%, 52.3%, 19.6%, 4.5%, 0.7% of EOC patients were diagnosed in 1, 2, 3, 4, and 5 encounters, respectively. Among the most frequent pathways to diagnosis, 22.0% of EOC patients had encountered a family physician and a Gynecologic Oncologist (GynOnc), 12.5% had one ER encounter, 9.3%, had an ER encounter followed by a GynOnc referral, 7.2% had encountered only a family physician prior to diagnosis, and 21% had an interaction with an Obstetrician/Gynecologist during their diagnostic interval. In the cases with 2 encounters, usually a family or emergency physician referred the patient to a GynOnc. In the cases with 1 encounter, typically a family or emergency physician diagnosed the patient prior to confirmation of diagnosis by a GynOnc. Half of the cohort was seen by a GynOnc prior to diagnosis (53.6%), and only 4.66% were never seen by a GynOnc.

Almost half of the study cohort was diagnosed within 30 days of first presentation (43.3% of all patients), and 62.6% were diagnosed within 60 days of first presentation (Figure 1). 74% of all patients had been diagnosed within 90 days of presentation with signs or symptoms of EOC, or after incidental finding on physical exam or imaging. Due to the expected difference in diagnostic interval in the ER versus non-ER setting, analyses for diagnostic, referral, and treatment intervals were stratified by ER status at first presentation. Significant differences in diagnostic, referral, and treatment intervals were seen between ER and non-ER patients. The median diagnostic interval for an ER patient was 7 days versus 55 days for non-ER patients (Figure 1; $p<0.0001$). The median referral interval for ER patients was 18 days, whereas it was 56 days for non-ER patients (Figure 2; $p=0.0063$). Time from first presentation to first treatment was very highly correlated with time from first presentation to diagnosis ($r > 0.95$; Supplemental Figure 1). Therefore, the treatment interval as an outcome was not investigated further.

To extend our analyses, we evaluated the ER and non-ER populations further to identify predictors related to diagnostic and referral intervals (Tables 2 and 3, respectively). However, most predictors as outlined in Table 1 were not statistically significant after multivariable analysis.

Survival was assessed to determine the impact of ER status and diagnostic interval (Figure 3). ER patients and patients with shorter diagnostic interval had significantly poorer survival. Predictors of ER presentation were also assessed (Table 4). The odds of a patient who presented in the ER having unclassified disease were also higher than that for a non-ER patient. Additionally, patients with high/very high comorbidities and patients with abdominal pain were more likely to first present in the ER (OR=3.028, CI[1.73-5.29], p=0.0001; OR=4.149, CI[2.44-7.07], p<0.0001, respectively), with a significant interaction between the two factors (OR=0.396, CI[0.17-0.91], p=0.0284) indicating that the effect of abdominal pain decreased if the patient had high/very high comorbidities. Urban residents were more likely to present at the ER than rural patients (OR=2.421, CI[1.60-3.67], p<0.0001).

INTERPRETATION

The majority of EOC cases in Manitoba from 2004-2010 were diagnosed within 2 encounters and 60 days of initial presentation. Amongst non-ER patients, presentation at earlier stage and without substantial comorbidities was associated with longer diagnostic intervals. Therefore, relatively healthy patients who present with less severe symptoms likely have less urgent investigations. EOC patients who presented to the ER were more likely to have more severe disease, more often demonstrated abdominal and respiratory symptoms, and likely prompted more aggressive investigations, with led to shorter diagnostic and referral intervals. The

diagnostic intervals were shorter than referral intervals, which is a reflection of other physicians diagnosing EOC before referral to subspecialists. These factors likely explain why EOC patients who presented to the ER had worse survival than those who presented elsewhere. Our data shows that the majority of cases are diagnosed within 60 days after 2 health care encounters of first presentation; only 5.16% of cases had 4 or more physician encounters before diagnosis.

One survey study found a median interval of 37 days from symptom onset to diagnosis [14], which is comparable to the results reported herein. Theoretically, faster diagnosis in the primary care setting would lead to earlier stage detection; however, the present study also found that first presentation in the ER and having shorter diagnostic interval are related to poorer survival. Similarly, in a study examining a cohort of adolescents and young adults with cancer, Xu *et al.* identified that having a first contact through an ER admission was related to lower survival, but that delays in the diagnostic interval or delay in treatment were not related to outcome [15]. Moreover, data from Nagle *et al.* suggests that a longer diagnostic interval for symptomatic women with invasive EOC does not adversely affect survival [16] and Robinson et al. (2012) found that increased pain scores was associated with worsened survival [17]; both studies were based on patient questionnaires and therefore open to recall bias Kirwan *et al.* showed how EOC survival was related to patient age and stage at diagnosis, but that delays in patient reporting and referral from primary care was not related to survival [18]. This was also supported by Menczer et al. (2009 & 2000) who found that duration of symptoms was not associated with prognostic factors [19, 20]. Our study supports the notion that a delay in diagnosis does not contribute to poorer outcomes, and found that the main factor affecting diagnostic and referral intervals, was presentation to the ER.

Multiple studies have examined screening and early detection showing that there is no benefit to overall survival. Gilbert *et al.* trialed open access CA-125 and ultrasound testing for

women with symptoms of EOC. The late stage cases detected had smaller, more resectable tumour volumes, with a larger proportion showing disease localized to the fallopian tube instead of having ovary involvement [21]. Findings from this study emphasize the need to detect disease at more resectable, lower volumes [21]. A 2010 publication showed that advanced cases of serous carcinoma (Type 2) had a shorter duration of symptoms compared to mucinous carcinoma (Type 1) [22]. This suggests that the late-stage diagnosis of serous carcinoma cases is likely due to rapid progression rather than delay in detection. One study found a mean 90.3 day interval from symptom onset to diagnosis [14], which is comparable to the results reported herein. Our study supports the previous literature showing that most patients are diagnosed within 90 days of presentation and that the diagnostic, referral, and treatment intervals are all closely related.

A strength of this study is the length of timelines of the patient journey were estimated from a combination of provincial physician billing data, hospital administration data and patient records, allowing us to use a combination "audit/database analysis" as described in Weller et al. (2012). These timelines were not based on questionnaires, thus avoided attempting to avoid patient recall bias [13]. We also examined diagnostic interval, referral interval and treatment interval and found that they were all highly correlated. One limitation of this study is that some analyses might have been underpowered, especially in calculating the effect of variables within the smaller ER patient population. Also, all relevant information may not have been recorded in the patient charts (e.g. all symptoms at all visits). Although avoiding recall bias using this method, gathering date of first presentation from patient records may not represent the "true" initial start of patient symptoms; the patient may also have presented to the health care system with other "charted" conditions, yet still suffered from the symptoms under question. It is unknown how long the patient had symptoms prior to initial presentation, however according to Tokuda et al. (2009) ovarian cancer has a symptom interval median of 15 days and mean of 38.5

days [23].

Our study has identified that the main factor associated with the diagnostic interval in EOC cases is the setting of the initial presentation (ER vs. non-ER). Patients who presented to the ER more likely had abdominal pain and respiratory symptoms, and possibly more aggressive disease. They were likely more rapidly investigated, leading to quicker diagnosis and referral, despite poorer prognosis. By contrast, those women presenting in the community with non-specific symptoms more often had considerably longer diagnostic and referral intervals, but better outcomes.Although it is important to emphasize EOC awareness and early detection by primary care practitioners in the community, improving the prognosis of EOC is a complex, evolving algorithm. One factor for EOC detection to be considered is the availability of primary care providers. In our cohort, it is possible that ER patients were less likely to have a regular family physician to whom they could present with symptoms, or for regular examinations. It would be useful to know the proportion of ER patients without a regular primary care provider and if there is an association with disease outcomes. The MOCO study group is further investigating treatment algorithms, primary care availability, and adjuvant therapies to determine effects on EOC patient outcomes.

ACKNOWLEDGEMENTS

The authors acknowledge the entire team at the Manitoba Cancer Registry and CancerCare Manitoba for their administrative support and hard work, especially Gail Noonan, Mary Natividad, Katie Galloway, Sara Gray, Lori Ann Love, Danielle Chalmers, and Grace Musto. AJL completed part of this research as a component of her B.Sc. Med thesis project under the supervision of ADA and MWN. This study was made possible by a CancerCare Manitoba Foundation operating grant to ADA, DT, and MWN. The results and conclusions are those of the authors and no official endorsement by Manitoba Health, Healthy Living and Seniors is intended or should be inferred.

REFERENCES

1. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in australia, canada, denmark, norway, sweden, and the UK, 1995-2007 (the international cancer benchmarking partnership): An analysis of population-based cancer registry data. Lancet. 2011 Jan 8;377(9760):127-38.

2. Canadian Cancer Society. Canadian cancer Society's advisory committee on cancer statistics. canadian cancer statistics 2015. Annual statistics report. Toronto: Canadian Cancer Society; 2015.

3. Department of Epidemiology and Cancer Registry. Cancer in manitoba, 2012 annual statistical report. Annual report. Manitoba: CancerCare Manitoba; 2012.

4. Heintz AP, Odicino F, Maisonneuve P, Beller U, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. Int J Gynaecol Obstet. 2003 Oct;83 Suppl 1:135-66.

5. Neville F. Hacker, MD, Joseph C. Gambone, DO and Calvin J. Hobel M. Ovarian cancer . In: Merrit J AC, editor. Essentials of Obstetrics and Gynecology. 5th ed. 5th ed. Philadelphia: Saunders Elsevier Inc.; 2010. p. 412.

6. Sorensen RD, Schnack TH, Karlsen MA, Hogdall CK. Serous ovarian, fallopian tube and primary peritoneal cancers: A common disease or separate entities - a systematic review. Gynecol Oncol. 2015 Mar;136(3):571-81.

7. Maringe C, Walters S, Butler J, Coleman MP, Hacker N, Hanna L, et al. Stage at diagnosis and ovarian cancer survival: Evidence from the international cancer benchmarking partnership. Gynecol Oncol. 2012 Oct;127(1):75-82.

8. Neal RD, Allgar VL, Ali N, Leese B, Heywood P, Proctor G, et al. Stage, survival and delays in lung, colorectal, prostate and ovarian cancer: Comparison between diagnostic routes. Br J Gen Pract. 2007 Mar;57(536):212-9.

9. Wikborn C, Pettersson F, Moberg PJ. Delay in diagnosis of epithelial ovarian cancer. Int J Gynaecol Obstet. 1996 Mar;52(3):263-7.

10. Lim A, Mesher D, Gentry-Maharaj A, Balogun N, Widschwendter M, Jacobs I, et al. Time to diagnosis of type I or II invasive epithelial ovarian cancers: A multicentre observational study using patient questionnaire and primary care records. BJOG. 2016 May;123(6):1012-20.

11. Brownell M, Mayer T, Martens PJ, Kozyrskyj A, Fergusson P, Bodnarchuk J, et al. Using a population-based health information system to study child health. Can J Public Health. 2002 Nov-Dec;93 Suppl 2:S9-14.

12. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? systematic review. Br J Cancer. 2015 Mar 31;112 Suppl 1:S92-107.

13. Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, et al. The aarhus statement: Improving design and reporting of studies on early cancer diagnosis. Br J Cancer. 2012 Mar 27;106(7):1262-7.

14. Allgar VL, Neal RD. Delays in the diagnosis of six cancers: Analysis of data from the national survey of NHS patients: Cancer. Br J Cancer. 2005 Jun 6;92(11):1959-70.

15. Xu Y, Stavrides-Eid M, Baig A, Cardoso M, Rho YS, Shams WM, et al. Quantifying treatment delays in adolescents and young adults with cancer at McGill university. Curr Oncol. 2015 Dec;22(6):e470-7.

16. Nagle CM, Francis JE, Nelson AE, Zorbas H, Luxford K, de Fazio A, et al. Reducing time to diagnosis does not improve outcomes for women with symptomatic ovarian cancer: A report from the australian ovarian cancer study group. J Clin Oncol. 2011 Jun 1;29(16):2253-8.

17. Robinson KM, Christensen KB, Ottesen B, Krasnik A. Diagnostic delay, quality of life and patient satisfaction among women diagnosed with endometrial or ovarian cancer: A nationwide danish study. Qual Life Res. 2012 Nov;21(9):1519-25.

18. Kirwan JM, Tincello DG, Herod JJ, Frost O, Kingston RE. Effect of delays in primary care referral on survival of women with epithelial ovarian cancer: Retrospective audit. BMJ. 2002 Jan 19;324(7330):148-51.

19. Menczer J. Diagnosis and treatment delay in gynecological malignancies. does it affect outcome? Int J Gynecol Cancer. 2000 Mar;10(2):89-94.

20. Menczer J, Chetrit A, Sadetzki S, National Israel Ovarian Cancer Group. The effect of symptom duration in epithelial ovarian cancer on prognostic factors. Arch Gynecol Obstet. 2009 Jun;279(6):797-801.

21. Gilbert L, Basso O, Sampalis J, Karp I, Martins C, Feng J, et al. Assessment of symptomatic women for early diagnosis of ovarian cancer: Results from the prospective DOvE pilot project. Lancet Oncol. 2012 Mar;13(3):285-91.

22. Lurie G, Wilkens LR, Thompson PJ, Matsuno RK, Carney ME, Goodman MT. Symptom presentation in invasive ovarian carcinoma by tumor histological type and grade in a multiethnic population: A case analysis. Gynecol Oncol. 2010 Nov;119(2):278-84.

23. Tokuda Y, Chinen K, Obara H, Joishy SK. Intervals between symptom onset and clinical presentation in cancer patients. Intern Med. 2009;48(11):899-905.

Table 1: Baseline characteristics and clinical features of patients by first presentation location (n=601).

		First presentation in the ER			
		No		Yes	
		N = 430		N = 171	
Variable		**Count**	**%**	**Count**	**%**
Age	mean (SD)	62.7	(13.7)	65.2	(16.1)
Stage	I	114	26.51	23	13.45
	II	56	13.02	17	9.94
	III	143	33.26	57	33.33
	IV	73	16.98	47	27.49
	Unknown	44	10.23	27	15.79
Histotype	Serous	175	40.70	48	28.07
	Unclassified	100	23.26	69	40.35
	Clear Cell	29	6.74	7	4.09
	Endometrioid	41	9.53	<6	<4%
	Mucinous	37	8.60	11	6.43
	Other	48	11.16	31	18.13
Type	I	96	22.33	24	14.04
	II	334	77.67	147	85.96
Residence	Urban	226	52.56	119	69.59
	Rural	204	47.44	52	30.41
Income	R1-R3	112	26.05	25	14.62
	R4-R5	73	16.98	20	11.70
	U1-U3	148	34.42	88	51.46
	U4-U5	92	21.40	32	18.71
	Missing	<6	<4%	<6	<4%
*R=rural; U=urban;					
Comorbidities (Resource utilization band)	Low	19	4.42	<6	<4%
	Moderate	287	66.74	91	53.22
	High	89	20.70	46	26.90
	Very High	35	8.14	28	16.37
Abdominal pain		144	33.49	91	53.22
Abdominal distension		118	27.44	61	35.67
Incidental		58	13.49	9	5.26
Bowel symptoms		36	8.37	20	11.70
Nausea		24	5.58	19	11.11
Decreased appetite		31	7.72	11	6.43

Respiratory symptoms	17	3.95	22	12.87
Weight change	26	6.05	10	5.85
Urinary symptoms	24	5.58	5	2.92
Abnormal bleeding	28	6.51	2	1.17
Postmenopausal bleeding	29	6.74	1	0.58
Palpable mass	22	5.12	4	2.34
Weakness	14	3.26	11	6.43
Emesis	12	2.79	12	7.02

Table 2: Multivariable quantile regression models predicting diagnostic intervals (in days) by ER status at initial presentation.

Presentation beginning in the ER				
		Median difference	**95% CI**	***p***
	(Intercept)	23.958	3.01 - 44.90	0.0252
Abdominal pain and emesis	Pain and no emesis	7.042	2.26 - 11.83	0.0042
	Pain and emesis	-1	-10.50 - 8.50	0.8356
	No pain or emesis	(reference)		
Type	II	-20.958	-41.88 - -0.03	0.0497
	I	(reference)		
Presentation beginning outside the ER				
		Median difference	**95% CI**	***p***
	(Intercept)	52.042	43.47 - 60.61	<0.0001
Stage	I/II	33.958	22.22 - 45.69	<0.0001
	III/IV	(reference)		
	Unknown	2.000	-16.26 - 20.26	0.8296
Abdominal distension	Yes	-28.042	-38.00 - -18.08	<0.0001
	No	reference)		
Postmenopausal bleeding	Yes	56.000	18.77 - 93.23	0.0033
	No	(reference)		

Table 3: Multivariable quantile regression models predicting referral intervals (in days) by ER status at initial presentation**.**

Presentation beginning in the ER				
		Median difference	**95% CI**	***p***
	(Intercept)	19.000	14.32 - 23.68	<0.0001
Abdominal distension	Yes	-7.000	-13.16 - -0.84	0.0262
	No	(reference)		
Presentation beginning outside the ER				
		Median difference	**95% CI**	***p***
	(Intercept)	68.958	59.03 - 78.89	<0.0001
Comorbidities (Resource utilization band)	High/Very High	-16.958	-27.53 - -6.39	0.0017
	Moderate and lower	(reference)		
Abdominal distension	Yes	-28.917	-39.95 - -17.88	<0.0001
	No	(reference)		

Table 4: Multivariable logistic regression model predicting patients that appear in the ER at first suspicion versus elsewhere.

		OR	95% CI	p
Morphology	Serous Carcinoma	0.393	0.24 - 0.64	0.0001
	Unclassified Epithelial	1		
	Clear Cell / Endometrioid	0.280	0.13 - 0.59	0.0007
	Mucinous	0.518	0.23 - 1.15	0.1052
	Other	0.906	0.50 - 1.65	0.7469
Residence	Winnipeg	2.421	1.60 - 3.67	<0.0001
	Non-Winnipeg	1		
Comorbidities (Resource utilization band)	High/Very High	3.028	1.73 - 5.29	0.0001
	Moderate and lower	1		
Abdominal pain	Yes	4.149	2.44 - 7.07	<0.0001
	No	1		
Respiratory symptoms	Yes	4.985	2.32 - 10.70	<0.0001
	No	1		
Abnormal bleeding	Yes	0.210	0.05 - 0.94	0.0416
	No	1		
Postmenopausal bleeding	Yes	0.120	0.02 - 0.93	0.0428
	No	1		
Interaction between comorbidities and abdominal pain		0.396	0.17 - 0.91	0.0284
		1		

*other epithelial-stromal, and miscellaneous and unspecified

Figure 1. Cumulative incidence of diagnosis for EOC patients presenting in the ER or elsewhere (Non-ER). Incidence of diagnosis was measured over time (days) from point of initial presentation. Patients presenting in the ER were diagnosed sooner than those presenting elsewhere.

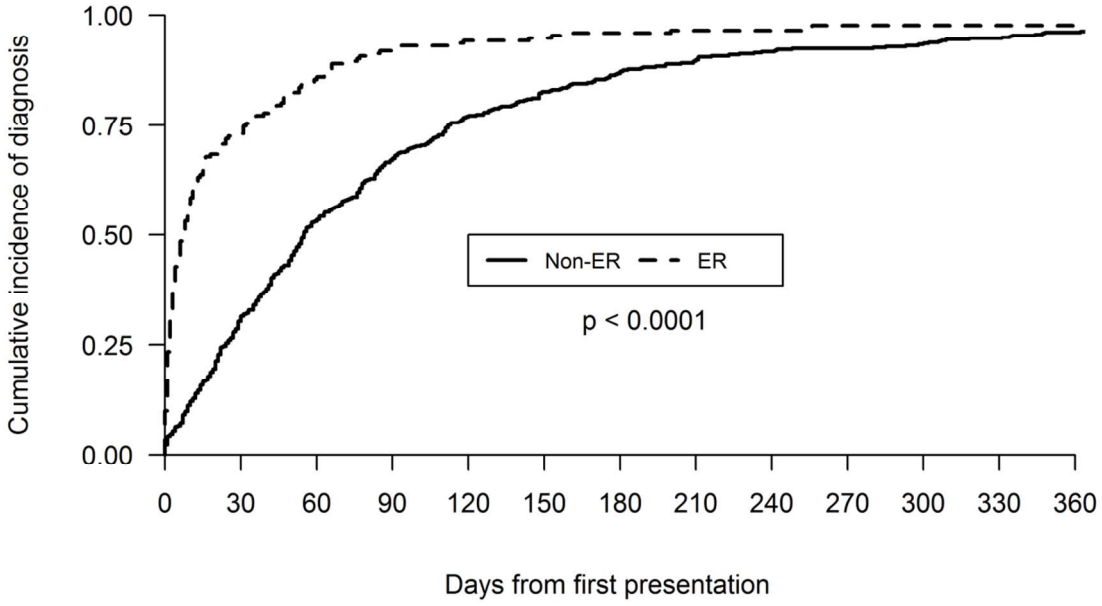
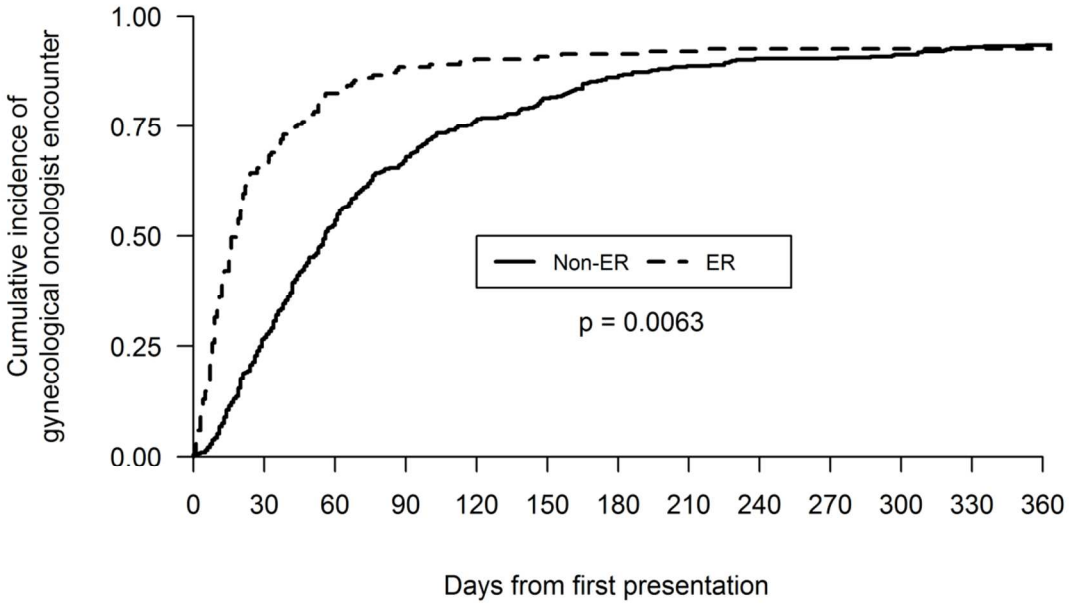


Figure 2. Cumulative incidence of GynOnc encounter for EOC patients presenting in the ER or elsewhere (Non-ER). Incidence of GynOnc referral was measured over time (days) from point of presentation. Similar to incidence of diagnosis, patients presenting in the ER were referred sooner than those presenting elsewhere.



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

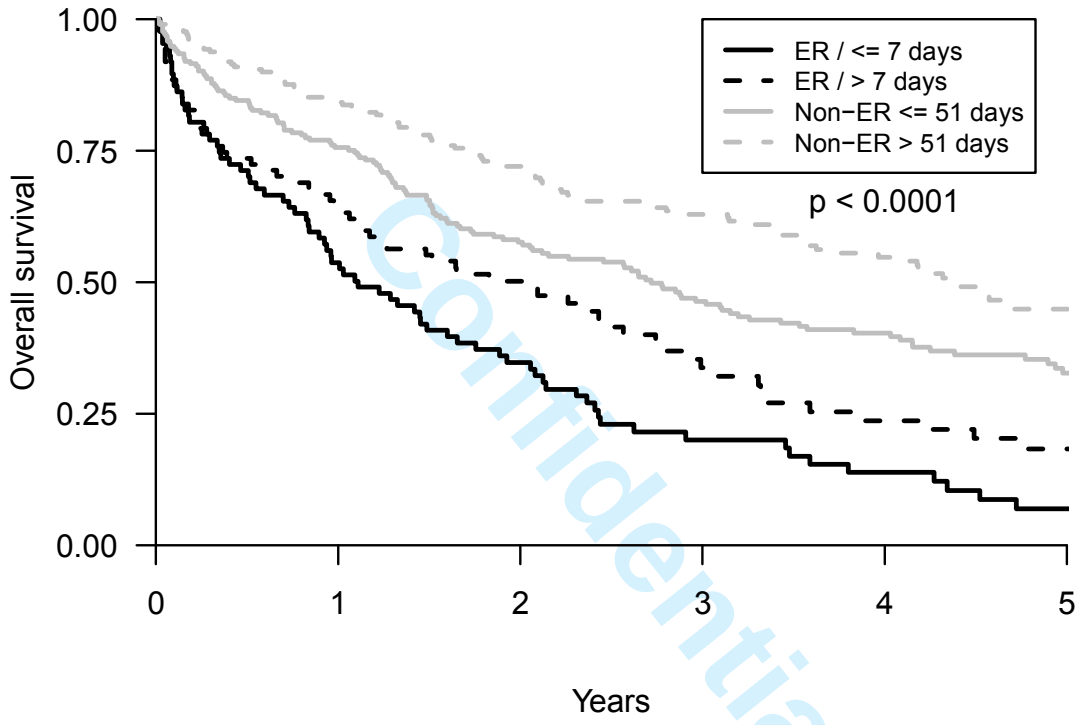
	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **pg 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **pg 2-3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **pg 4**
Objectives	3	State specific objectives, including any prespecified hypotheses **pg 4**
Methods		
Study design	4	Present key elements of study design early in the paper **pg 4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **pg 4**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **pg 5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **pg 5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **pg 5-6**
Bias	9	Describe any efforts to address potential sources of bias **pg 5**
Study size	10	Explain how the study size was arrived at **pg 4-5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **pg 5-6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **pg 5-6**
		(*b*) Describe any methods used to examine subgroups and interactions **pg 5-6**
		(*c*) Explain how missing data were addressed **n/a**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **n/a**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **pg 6**
		(b) Give reasons for non-participation at each stage **pg 6**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **pg 6 and Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **pg 6 and Table 1**
Outcome data	15*	Report numbers of outcome events or summary measures **pg 6-8**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Supplemental table, Table 2-4**
		(*b*) Report category boundaries when continuous variables were categorized

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **n/a**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Interaction terms**
Discussion		
Key results	18	Summarise key results with reference to study objectives **pg 8**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **pg 10**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **pg 10**
Generalisability	21	Discuss the generalisability (external validity) of the study results **pg 10**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **pg 1**

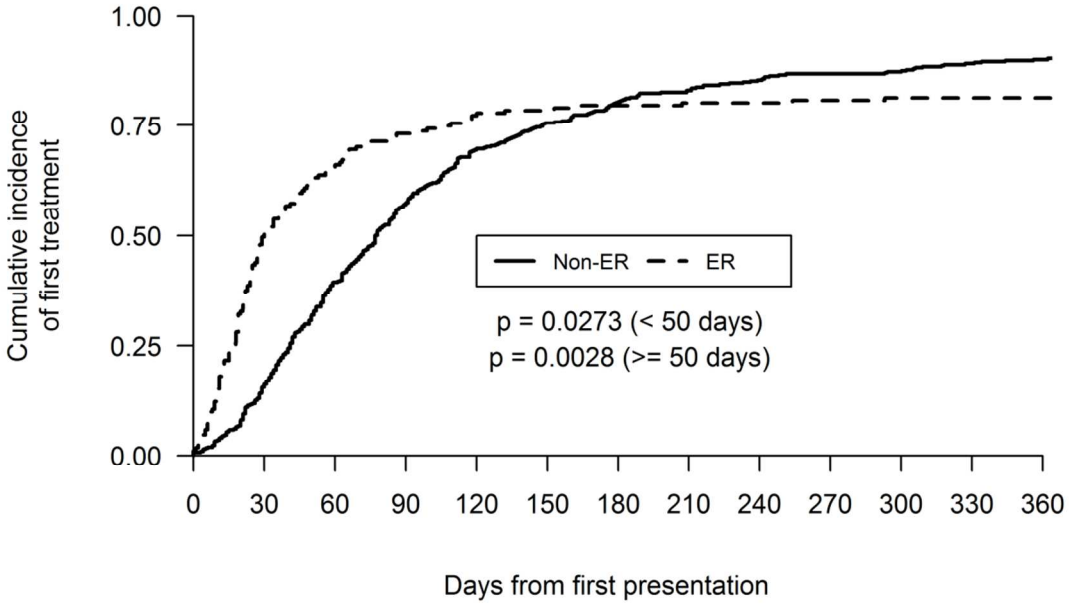
*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Figure 3. Kaplan-Meier curve illustrating overall survival for EOC patients presenting in the emergency room (ER) or elsewhere (Non-ER). ER patients exhibited poorer survival than non-ER patients. "Days" indicates median diagnostic interval.



Supplemental Figure 1



Supplemental Figure 1. Cumulative incidence of first treatment for EOC patients presenting in the ER or elsewhere (Non-ER). Incidence of first treatment (date of first chemotherapy dose, or date of surgery) was measured over time (days) from point of presentation. Similar to incidence of GynOnc encounter, patients presenting in the ER initiated treatment sooner than those presenting elsewhere.

Supplemental Table 1: Univariable quantile regression models predicting diagnostic intervals for patients first presenting in the ER (in days)

			Median difference	95% CI	p
	Intercept		3.848	-10.99 - 18.69	0.6094
Age	(per 10 years)		0.494	-1.57 - 2.56	0.6369
	Intercept		6.000	2.40 - 9.60	0.0012
Stage	I/II		16.000	-4.59 - 36.59	0.1270
	III/IV		(reference)		
	Unknown		0.000	-5.70 - 5.70	1.0000
	Intercept		6.000	2.07 - 9.93	0.0030
Morphology	Serous Carcinoma		0.000	-6.55 - 6.55	1.0000
	Unclassified Epithelial		(reference)		
	Clear Cell / Endometrioid		25.000	-3.47 - 53.47	0.0849
	Mucinous		9.000	-16.30 - 34.30	0.4835
	Other		-2.000	-9.53 - 5.53	0.6006
	*other epithelial-stromal, and miscellaneous and unspecified				
	Intercept		10.000	-0.63 - 20.63	0.0651
Residence	Winnipeg		-3.000	-14.14 - 8.14	0.5955
	Non-Winnipeg		(reference)		
	Intercept		7.000	3.83 - 10.17	<.0001
Period of diagnosis	2008 and later		1.000	-4.52 - 6.52	0.7211
	2007 and earlier		(reference)		
Income	*Contrasts*				
	R4-R5 vs R1-R3		-7.958	-31.25 - 15.34	0.5009
	U4-U5 vs U1-U3		-3.000	-8.92 - 2.92	0.3188
*R=rural; U=urban; 1=poorest;5=richest					

	Intercept		6.000	2.73 - 9.27	0.0004
Comorbidities	High/Very High		-3.000	-2.70 - 8.70	0.2999
(Resource utilization	Moderate and lower		(reference)		
band)					
	Intercept		10.042	3.45 - 16.63	0.0030
Abdominal distension	Yes		-5.042	-12.34 - 2.26	0.1747
	No		(reference)		
	Intercept		7.000	3.78 - 10.22	<.0001
Incidental	Yes		6.000	-101.63 - 113.63	0.9125
	No		(reference)		
	Intercept		8.000	4.13 - 11.87	0.0001
Bowel symptoms	Yes		-4.000	-9.44 - 1.44	0.1485
	No		(reference)		
	Intercept		8.000	4.41 - 11.59	<.0001
Nausea	Yes		-5.000	-9.04 - -0.96	0.0156
	No		(reference)		
	Intercept		8.000	4.56 - 11.44	<.0001
Decreased appetite	Yes		-6.000	-10.20 - -1.80	0.0054
	No		(reference)		
	Intercept		8.000	4.27 - 11.73	<.0001
Respiratory symptoms	Yes		-3.000	-9.57 - 3.57	0.3686
	No		(reference)		
	Intercept		8.000	4.96 - 11.04	<.0001

Weight change	Yes		-6.000	-11.95 - -0.05	0.0480
	No		(reference)		
	Intercept		7.000	4.13 - 9.87	<.0001
Urinary symptoms	Yes		17.000	-26.08 - 60.08	0.4370
	No		(reference)		
	Intercept		-		
Abnormal bleeding	Yes		-		
	No		-		
	Intercept		-		
Postmenopausal	Yes		-		
bleeding	No		-		
	Intercept		7.958	5.04 - 10.87	<.0001
Palpable mass	Yes		-4.958	-16.20 - 6.28	0.3852
	No		(reference)		
Intercept			8.000	4.75 - 11.25	<.0001
Weakness	Yes		-5.000	-10.75 - 0.75	0.0878
	No		(reference)		
	Intercept		4.000	1.82 - 6.18	0.0004
Abdominal pain and vomiting	Pain and no emesis		7.000	2.26 - 11.74	0.0040
and emesis	Pain and emesis		-2.000	-4.69 - 0.69	0.1434
	No pain or emesis		(reference)		

Supplemental Table 2: Univariable quantile regression models predicting diagnostic intervals for patients first presenting outside the ER (in days)

			Median difference	95% CI	p
Intercept			61.850	18.33 - 105.37	0.0055
Age	(per 10 years)		-1.063	-7.85 - 5.73	0.7584
Intercept			42.000	34.06 - 49.94	<.0001
Stage	I/II		45.000	30.04 - 59.96	<.0001
	III/IV		(reference)		
	Unknown		12.000	-7.95 - 31.95	0.2377
Intercept			35.000	23.55 - 46.45	<.0001
Morphology	Serous Carcinoma		22.958	4.93 - 40.99	0.0127
	Unclassified Epithelial		(reference)		
	Clear Cell / Endometrioid		49.958	27.53 - 72.38	<.0001
	Mucinous		19.042	-14.10 - 52.18	0.2594
	Other		20.000	-1.93 - 41.93	0.0737
	*other epithelial-stromal, and miscellaneous and unspecified				
Intercept			49.000	39.42 - 58.58	<.0001
Residence	Winnipeg		12.042	-6.70 - 30.78	0.2073
	Non-Winnipeg		(reference)		
Intercept			53.000	46.61 - 59.39	<.0001
Period of diagnosis	2008 and later		15.958	-1.55 - 33.46	0.0738
	2007 and earlier		(reference)		
Income	*Contrasts*				
	R4-R5 vs R1-R3		11.000	-8.85 - 30.85	0.2767

	U4-U5 vs U1-U3		-0.958	-33.14 - 31.22	0.9533
*R=rural; U=urban; 1=poorest;5=richest					
Intercept			57.958	48.42 - 67.50	<.0001
Comorbidities	High/Very High		-10.958	-26.94 - 5.03	0.1786
(Resource utilization	Moderate and lower		(reference)		
band)					
Intercept			54.958	47.16 - 62.76	<.0001
Abdominal pain	Yes		1.042	-12.06 - 14.14	0.8759
	No		(reference)		
Intercept			75.958	62.05 - 89.86	<.0001
Abdominal distension	Yes		-43.000	-60.70 - -25.30	<.0001
	No		(reference)		
Intercept			54.000	48.93 - 59.07	<.0001
Incidental	Yes		29.042	-7.85 - 65.93	0.1225
	No		(reference)		
Intercept			55.042	48.56 - 61.52	<.0001
Bowel symptoms	Yes		-5.042	-32.96 - 22.87	0.7228
	No		(reference)		
Intercept			55.042	48.54 - 61.54	<.0001
Nausea	Yes		-8.042	-36.50 - 20.41	0.5789
	No		(reference)		
Intercept			57.958	50.04 - 65.88	<.0001
Decreased appetite	Yes		-26.958	-46.87 - -7.04	0.0081
	No		(reference)		

Intercept			56.000	48.88 - 63.12	<.0001
Respiratory symptoms	Yes		-14.000	-37.17 - 9.17	0.2356
	No		(reference)		
Intercept			56.000	48.93 - 63.07	<.0001
Weight change	Yes		-13.000	-35.17 - 9.17	0.2497
	No		(reference)		
Intercept			54.958	48.65 - 61.27	<.0001
Urinary symptoms	Yes		4.083	-48.09 - 56.26	0.8778
	No		(reference)		
Intercept			55.000	49.67 - 60.33	<.0001
Abnormal bleeding	Yes		29.958	-29.57 - 89.48	0.3231
	No		(reference)		
Intercept			53.000	47.84 - 58.16	<.0001
Postmenopausal	Yes		74.958	28.17 - 121.64	0.0017
bleeding	No		(reference)		
Intercept			55.000	49.02 - 60.98	<.0001
Palpable mass	Yes		0.000	-34.44 - 34.44	1.0000
	No		(reference)		
Intercept			55.042	47.83 - 62.25	<.0001
Weakness	Yes		-8.042	-34.81 - 18.73	0.5552
	No		(reference)		
Intercept			55.958	48.68 - 63.24	<.0001
Vomiting	Yes		-37.958	-63.47 - -12.45	0.0036

	No		(reference)		

Supplemental Table 3: Univariable quantile regression models predicting referral intervals for patients first presenting in the ER (in days)

			Median difference	95% CI	p
Intercept			13.152	-6.65 - 32.95	0.1915
Age	(per 10 years)		0.389	-2.43 - 3.21	0.7853
Intercept			12.000	8.27 - 15.73	<.0001
Stage	I/II		8.000	-0.65 - 16.65	0.0696
	III/IV		(reference)		
	Unknown		9.000	-4.02 - 22.02	0.1739
Intercept			19.000	14.47 - 23.53	<.0001
Morphology	Serous Carcinoma		-7.000	-13.84 - -0.16	0.0448
	Unclassified Epithelial		(reference)		
	Clear Cell / Endometrioid		2.000	-15.08 - 19.08	0.8174
	Mucinous		-3.000	-24.16 - 18.16	0.7798
	Other		-0.042	-10.07 - 9.98	0.9935
	*other epithelial-stromal, and miscellaneous and unspecified				
Intercept			21.000	11.83 - 30.17	<.0001
Residence	Winnipeg		-6.000	-16.08 - 4.08	0.2413
	Non-Winnipeg		(reference)		
Intercept			13.000	9.04 - 16.96	<.0001
Period of diagnosis	2008 and later		6.000	-0.51 - 12.51	0.0704
	2007 and earlier		(reference)		
Income	*Contrasts*				
	R4-R5 vs R1-R3		2.958	-21.94 - 27.86	0.8148

	U4-U5 vs U1-U3		-3.000	-11.95 - 5.95	0.5087
*R=rural; U=urban; 1=poorest;5=richest					
Intercept			16.000	11.73 - 20.27	<.0001
Comorbidities	High/Very High		0.000	-7.64 - 7.64	1.0000
(Resource utilization	Moderate and lower		(reference)		
band)					
Intercept			16.000	11.81 - 20.19	<.0001
Abdominal pain	Yes		-1.000	-8.77 - 6.77	0.7996
	No		(reference)		
Intercept			19.000	14.32 - 23.68	<.0001
Abdominal distension	Yes		-7.000	-13.16 - -0.84	0.0262
	No		(reference)		
Intercept			15.000	11.48 - 18.52	<.0001
Incidental	Yes		4.000	-26.34 - 34.34	0.7949
	No		(reference)		
Intercept			16.000	11.89 - 20.11	<.0001
Bowel symptoms	Yes		-4.000	-15.46 - 7.46	0.4916
	No		(reference)		
Intercept			16.000	12.16 - 19.84	<.0001
Nausea	Yes		-6.000	-15.12 - 3.12	0.1957
	No		(reference)		
Intercept			16.000	12.16 - 19.84	<.0001
Decreased appetite	Yes		-7.000	-17.97 - 3.97	0.2095
	No		(reference)		

Intercept			16.000	11.71 - 20.29	<.0001
Respiratory symptoms	Yes		0.000	-7.96 - 7.96	1.0000
	No		(reference)		
Intercept			16.000	12.74 - 19.26	<.0001
Weight change	Yes		-7.000	-28.32 - 14.32	0.5177
	No		(reference)		
Intercept			16.000	12.38 - 19.62	<.0001
Urinary symptoms	Yes		-7.000	-45.92 - 31.92	0.7229
	No		(reference)		
Intercept			-		
Abnormal bleeding	Yes		-		
	No		-		
Intercept			-		
Postmenopausal	Yes		-		
bleeding	No		-		
Intercept			16.000	11.94 - 20.06	<.0001
Palpable mass	Yes		-1.000	-13.76 - 11.76	0.8772
	No		(reference)		
Intercept			16.000	12.84 - 19.16	<.0001
Weakness	Yes		-3.958	-22.65 - 14.74	0.6763
	No		(reference)		

Intercept			16.000	12.06 - 19.94	<.0001
Vomiting	Yes		-1.000	-13.32 - 11.32	0.8728
	No		(reference)		

Supplemental Table 4: Univariable quantile regression models predicting referral intervals for patients first presenting outside the ER (in days)

			Median difference	95% CI	p
Intercept			64.563	33.26 - 95.87	0.0001
Age	(per 10 years)		-1.565	-6.43 - 3.29	0.5270
Intercept			43.000	35.82 - 50.18	<.0001
Stage	I/II		18.000	6.96 - 29.04	0.0015
	III/IV		(reference)		
	Unknown		32.958	6.05 - 59.87	0.0165
Intercept			53.000	38.64 - 67.36	<.0001
Morphology	Serous Carcinoma		-3.958	-20.74 - 12.82	0.6431
	Unclassified Epithelial		(reference)		
	Clear Cell / Endometrioid		7.000	-16.97 - 30.97	0.5662
	Mucinous		17.042	-6.28 - 40.36	0.1517
	Other		3.042	-23.50 - 29.58	0.8218
	*other epithelial-stromal, and miscellaneous and unspecified				
Intercept			54.958	45.47 - 64.45	<.0001
Residence	Winnipeg		0.000	-12.10 - 12.10	1.0000
	Non-Winnipeg		(reference)		
Intercept			49.042	41.09 - 56.99	<.0001
Period of diagnosis	2008 and later		11.958	-1.73 - 25.64	0.0866
	2007 and earlier		(reference)		
Income	*Contrasts*				
	R4-R5 vs R1-R3		-3.000	-21.83 - 15.83	0.7526
	U4-U5 vs U1-U3		-1.000	-16.04 - 14.04	0.8960
*R=rural; U=urban; 1=poorest;5=richest					

Intercept			59.000	53.03 - 64.97	<.0001
Comorbidities	High/Very High		-15.000	-25.24 - -4.76	0.0042
(Resource utilization	Moderate and lower		(reference)		
band)					
Intercept			56.000	49.17 - 62.83	<.0001
Abdominal pain	Yes		-3.000	-14.78 - 8.78	0.6169
	No		(reference)		
Intercept			62.000	54.59 - 69.41	<.0001
Abdominal distension	Yes		-28.000	-39.44 - -16.56	<.0001
	No		(reference)		
Intercept			53.000	46.23 - 59.77	<.0001
Incidental	Yes		13.958	-6.29 - 34.20	0.1761
	No		(reference)		
Intercept			54.958	48.87 - 61.05	<.0001
Bowel symptoms	Yes		0.042	-21.01 - 21.09	0.9969
	No		(reference)		
Intercept			54.958	49.30 - 60.62	<.0001
Nausea	Yes		-7.958	-28.14 - 12.22	0.4387
	No		(reference)		
Intercept			56.000	49.99 - 62.01	<.0001
Decreased appetite	Yes		-14.000	-25.00 - -3.00	0.0127
	No		(reference)		
Intercept			54.958	48.80 - 61.12	<.0001

Respiratory symptoms	Yes		2.000	-28.39 - 32.39	0.8971
	No		(reference)		
Intercept			55.000	49.33 - 60.67	<.0001
Weight change	Yes		-9.000	-19.70 - 1.70	0.0990
	No		(reference)		
Intercept			55.000	49.48 - 60.52	<.0001
Urinary symptoms	Yes		-14.000	-48.14 - 20.14	0.4207
	No		(reference)		
Intercept			54.958	50.02 - 59.90	<.0001
Abnormal bleeding	Yes		7.083	-29.86 - 44.02	0.7064
	No		(reference)		
Intercept			53.000	46.42 - 59.58	<.0001
Postmenopausal	Yes		41.958	-11.13 - 95.05	0.1210
bleeding	No		(reference)		
Intercept			55.000	49.13 - 60.87	<.0001
Palpable mass	Yes		-2.000	-15.96 - 11.96	0.7783
	No		(reference)		
Intercept			55.000	49.21 - 60.79	<.0001
Weakness	Yes		-11.000	-26.94 - 4.94	0.1757
	No		(reference)		
Intercept			54.958	48.51 - 61.40	<.0001
Vomiting	Yes		-3.958	-30.28 - 22.37	0.7677
	No		(reference)		

Supplemental Table 5: Univariable logistic regression models predicting first presentation in the ER

			OR	95% CI	p
Variable					
Age	'		0.974	0.95 - 1.00	0.0012
	"		1.054	1.02 - 1.09	
Stage	I/II		0.489	0.32 - 0.74	0.0007
	III/IV		1		
	Unknown		1.275	0.75 - 2.17	0.3727
Morphology	Serous Carcinoma		0.398	0.13 - 0.49	<.0001
	Unclassified Epithelial		1		
	Clear Cell / Endometrioid		0.248	0.13 - 0.49	<.0001
	Mucinous		0.431	0.21 - 0.90	0.0257
	Other		0.936	0.54 - 1.62	0.8123
	*other epithelial-stromal, and miscellaneous and unspecified				
Residence	Winnipeg		2.066	1.42 - 3.01	0.0002
	Non-Winnipeg		1		
Period of diagnosis	2008 and later		1.310	0.92 - 1.87	0.1370
	2007 and earlier		1		
Income	*Contrasts*				

	R4-R5 vs R1-R3		1.227	0.64 - 2.37	0.5415
	U4-U5 vs U1-U3		0.585	0.36 - 0.95	0.0289
*R=rural; U=urban; 1=poorest;5=richest					
Comorbidities	High/Very High		1.883	1.30 - 2.72	0.0007
(Resource utilization	Moderate and lower		1		
band)					
Abdominal pain	Yes		2.259	1.58 - 2.72	<.0001
	No		1		
Abdominal distension	Yes		1.466	1.00 - 2.14	0.0471
	No		1		
Incidental	Yes		0.356	0.17 - 0.74	0.0053
	No		1		
Bowel symptoms	Yes		1.450	0.81 - 2.58	0.2080
	No		1		
Nausea	Yes		2.115	1.13 - 3.97	0.0198
	No		1		
Decreased appetite	Yes		0.885	0.43 - 1.80	0.7363
	No		1		
Respiratory symptoms	Yes		3.587	1.85 - 6.94	0.0001
	No		1		
Weight change	Yes		0.965	0.46 - 2.05	0.9263
	No		1		

Urinary symptoms	Yes		0.510	0.19 - 1.36	0.1776
	No		1		
Abnormal bleeding	Yes		0.170	0.04 - 0.72	0.0163
	No		1		
Postmenopausal	Yes		0.081	0.01 - 0.60	0.0140
bleeding	No		1		
Palpable mass	Yes		0.444	0.15 - 1.31	0.1410
	No		1		
Weakness	Yes		2.043	0.91 - 4.59	0.0841
	No		1		
Vomiting	Yes		2.629	1.16 - 5.97	0.0210
	No		1		

2016-11-06

Author response:

To Erin Russell, the editorial board and reviewers:

Thank you very much for reviewing our paper and for the insightful comments. We have made several revisions to the research paper itself in response to the reviewer concerns, and have remarked on the reviewer's comments below. In response to the reviewers comments, we cite the lines in the "clean" version of the revised text. Please let us know if any further revisions are necessary, or if any confusion remains.

Sincerely,

Alon Altman MD, FRCSC

1. Methods: Subheadings (e.g., setting, design, sources of data, statistical analysis) are helpful for readers.

- The above mentioned sections have been added to our methods.

2. Statistical analyses: How were predictor variables selected? Was any attempt made to test for interaction between predictor variables?

- The predictor variables shown were chosen based on availability and previously identified prognostic effects (e.g. histotype, grade, age, stage, etc.) and effects that we were specifically investigating (e.g. distance, urban/rural, socioeconomic status). Likelihood ratio testing was used to select variables to be kept in the multivariable analysis (indicated in lines 124-125). Interaction terms have now been tested, and we have found a significant interaction for the analysis in Table 4.

3. Results: Please include all predictor variables in Tables 2/3.

- Within the manuscript this would have extended the paper beyond the dictated limits. We have included it as an appendix/supplemental. In response to the editor's comments, we have included these tables as Supplemental tables 1-5.

4. Interpretation: Please elaborate on your limitations section to address reviewer concerns below (e.g., the limited validity of data extracted from patient charts, particularly the 'date of suspicion').

- See below, Reviewer 3 comment 1.

5. Please include a completed reporting guideline checklist (i.e., STROBE).

- STROBE guideline checklist attached

Manuscript requirements:

1. Please include study type in your title.

- We have now included this in the title. See line 5

2. Abstract: CMAJ Open requires a structured abstract of no more than 250 words that contains the following sections:
a. Background: Includes a clear statement of the study aim and research question. (2 sentences)
b. Methods: Includes the research design, setting of the study, and participants, including number participating and criteria for selection, entry and exclusion. The interventions, if applicable, should be clearly outlined, as well as primary and secondary outcome measures.
c. Results: The main findings should be quantified with 95% confidence intervals and the number needed to treat or harm, if applicable. Absolute, rather than relative, risks are preferable.
d. Interpretation: This should include the main conclusions and implications. (2 sentences)

- The abstract has been amended to follow these guidelines

3. Introduction: Please ensure this is no longer than 2 paragraphs. A statement of the study aim and research question should be included at the end of the introduction.

- We are compliant with this instruction

4. Interpretation: Please include the following 4 main categories: main findings (1 paragraph); explanation and comparison with other studies (2 paragraphs); limitations (1 paragraph); and conclusions and implications for practice and future research (1 paragraph).

- We are compliant with this instruction

5. Abbreviations: For only the most standard abbreviations (i.e., 95% CI, SD, OR, RR, HR), please spell out at first mention and include the abbreviation in parentheses. The abbreviations may be used throughout the remainder of the manuscript. Please remove all other abbreviations.

- We are compliant with this instruction

6. Please include up to 1 academic and 1 professional degree after each author's name.

- We are compliant with this instruction

Peer review comments:

Reviewer 1: Dr. Prafull Ghatage, University of Calgary, Gynecologic Oncology

Interesting paper. however, it would add strength to this paper if there was a table comparing ER and non-ER patients with reference to differences Stage, Histology,survival,age aside from presentation.

- We have replaced table 1 with this recommendation

Reviewer 2: Dr. James Bentley, Dalhousie University, Department of Obstetrics and Gynecology

This retrospective review of referral and diagnosis provides useful information.
1. At no point in the discussion of referral pathways was the role of the generalist OB Gyn noted. This deserves a mention even if it was not a factor, it would be nice to know for resource planning which cases were triaged in some way by a generalist?

- This information was added to Line 143: "21% had an interaction with an Obstetrician/Gynecologist during their diagnostic interval"

2. I noted that there were 601 cases and in the results section it says that in total 469 had an initial diagnosis made +/- confirmed by histology. However in table 1 all 601 have a histotype classification. Can you clarify this?

- The 469 patients were diagnosed by histology. The remaining patients did not have final confirmation and were treated based on cytology. This was clarified in line 134-137: "Subsequent diagnostic confirmation by histology was seen in an additional 182 cases, yielding 469 patients (78.04%) overall with diagnosis confirmed on histology, the remaining patients were not confirmed by final histology, and were treated based on cytology alone."

Reviewer 3: Dr. VL Allgar, York University, HYMS/Health Sciences

1. Date of suspicion was recorded as first point of contact with a health care provider with symptoms of

EOC, or where there was incidental finding of EOC. This doesn't include patient delay e.g. patient recognition of suspicion prior to first contact.

- We absolutely agree with this statement and is an operational definition. We decided to balance the benefits of patient recall with definitive medical records data. The data prior to presentation is not available. We have included this as a clarified limitation in our paper (Line 225-231)

2. There are no univariate statistical tests of each factor with time from suspicion to diagnosis (page 6, para 2). E.g. factors in Table 1

- Due to table size and page limitations, the Univariate analysis was excluded. We have now included it as supplemental tables 1-5.

3. The median diagnostic interval for an ER patient was 7 days versus 55 days for non-ER patients, this is not surprising but was it statistically significant?

- This value was included in the figures, but not included in the text. We have corrected this and added the p value in line 156.

4. The paper then focuses on comparing ER patient versus non-ER patients. Whilst the analysis is appropriate, this should be reflected in the objectives of the paper and in the title. There should be a descriptive table with the variables split by ER - non ER and univariate analyses.

- The variables for ER vs non-ER have been adjusted as outlined above (see revised Table 1). ER status was not the initial objective of the study, and was found to be a significant variable on analysis. The discussion about ER status is extended because of the substantial difference noted in patient outcome and time-to-diagnosis.

Reviewer 4: Prof. Richard D. Neal, University of Leeds, Institute of Health Sciences

Introduction

1. Much important and relevant literature, including the findings of two systematic reviews, is not included. This includes:

♣ Smith EM, Anderson B (1985) The effects of symptoms and delay in seeking diagnosis on stage of disease at diagnosis among women with cancers of the ovary. Cancer 56: 2727–2732.

♣ Tokuda Y, Chinen K, Obara H, Joishy SK (2009) Intervals between symptom onset and clinical presentation in cancer patients. Intern Med 48: 899–905.

♣ Fruchter RG, Boyce J (1981) Delays in diagnosis and stage of disease in gynecologic cancer. Cancer Detect Prev 4: 481–486.

♣ Menczer J (2000) Diagnosis and treatment delay in gynaecological malignancies: does it affect

outcome? Int J Gynecol Cancer 10: 89–94.

♣ Menczer J, Chetrit A, Sadetzki S (2009) The effect of symptom duration in epithelial ovarian

♣ Robinson KM, Christensen KB, Ottesen B, Krasnik A (2012) Diagnostic delay, quality of life and patient satisfaction among women diagnosed with endometrial or ovarian cancer: a nationwide Danish study. Qual Life Res 21: 1519–1525.

♣ Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, Hamilton W, Hendry A, Hendry M, Lewis R, Macleod U, Mitchell ED, Pickett M, Rai T, Shaw K, Stuart N, Tørring ML, Wilkinson C, Williams B, Williams N, Emery J. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. British Journal of Cancer 2015, 1–16 doi: 10.1038/bjc.2015.48

This feels like a major omission, and one that has prevented them from framing their study in an appropriate context.

- The main objective of our study was to identify various factors affecting the diagnostic and referral intervals. We have clarified the definitions to be consistent with the literature as noted above. Please see the comments below for question 2.

- All of the suggested studies have been reviewed and information that was felt to be relevant was added to our discussion (Line 196-231)

2. Furthermore some of these older studies are of poor quality and there is much to learn from more recent studies (albeit in other cancers) that have examined time intervals to diagnosis and their association with clinical outcomes, and using methods that avoid some of the bias and confounding that these studies are open too. Examples of these include:

♣ Elit L, O'Leary E, Pond G, Seow H (2013) Impact of wait times on survival for women with uterine cancer. J Clin Oncol 51: 67.

♣ Gobbi PG, Bergonzi M, Comelli M, Villano L, Pozzoli D, Vanoli A, Dionigi P (2013) The prognostic role of time to diagnosis and presenting symptoms in patients with pancreatic cancer. Cancer Epidemiol 37: 186–190.

♣ Murchie P, Raja EA, Brewster DH, Campbell NC, Ritchie LD, Robertson R, Samuel L, Gray N, Lee AJ (2014) Time from presentation in primary care to treatment of symptomatic colorectal cancer: effect on disease stage and survival. Br J Cancer 111: 461–469.

♣ Tørring ML, Frydenberg M, Hamilton W, Hansen RP, Lautrup MD, Vedsted P (2012) Diagnostic interval and mortality in colorectal cancer: U-shaped association demonstrated for three different datasets. J Clin Epidemiol 65: 669–678.

♣ Tørring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P (2013) Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. Eur J Cancer 49(9): 2187–2198.

As a consequence the study that is reported here is open to biases and consequences, and therefore its findings must be interpreted with great caution, and do not take forwards our understanding of this issue.

- We respect and appreciate the reviewer's comments as such we have refined the definition of time-to-diagnosis, as: "Date of first presentation was recorded as first point of contact with a health care provider with symptoms of EOC, or where there was incidental finding of EOC. Date of referral encounter was recorded as the initial GynOnc appointment. Diagnostic interval was defined as the time from date of first presentation to diagnosis and the referral interval was defined as the date of first presentation to initial GynOnc visit." Line 104-110, and have quoted the Weller and Neal papers to refine the definitions used and be more consistent with the literature. While not using the same language our definition is consistent with the definition of T7 and T8 in Neal et. al. *British Journal of Cancer* 2015.
- We also analyzed what was considered T9 in the Neal et al. (2015) paper and found that in our population this was highly correlated to T7 and T8, and therefore no further description was provided (lines 157-159)
- The above noted trials were not referenced in our paper because we felt that the relevance from other cancers does not directly translate to the challenges posed in ovarian cancer diagnosis. For example, both colorectal and endometrial cancers present with more obvious symptoms with earlier stage disease.
- We agree that this study is open to bias, as are all retrospective chart reviews. We have expanded the limitations section to better delineate these limitation (line 222-231). To reduce bias we avoided patient recall and supplemented the chart data with administrative health care data from the provincial health database including physician claims and hospital administrative data (line 100-108), which added expanded time compared to the chart alone data, increasing accuracy. To be more comprehensive we analyzed diagnostic, referral and treatment intervals to assure that all were correlated and not another source of bias.

3. There is also a consensus statement on the design and reporting of studies on early cancer diagnosis:
Weller D, Vedsted P, Rubin G, Walter F, Emery J, Scott S, Campbell C, Andersen RS, Hamilton W, Olesen F, Rose P, Nafees S, van Rijswijk E, Muth C, Beyer M, Neal RD. The Aarhus Statement: Improving design and reporting of studies on early cancer diagnosis. BJC 2012,106:1262-1267. DOI 10.1038/bjc.2012.68.
Whilst it is not a necessity of this journal for authors to report their work in line with this, it does mean that their definitions are not in keeping with other recently published literature.

- Given the above changes, we are now compliant with the Aarhus definitions and have revised the limitations statement in this study. We have also clarified our definitions of date of first contact, date of diagnosis and date of death. We have also clarified that our study is a combined "audit/database analysis" as outlined in the Weller paper (line 219).

Key examples of text in the manuscript that reflect the difficulties with this paper include:
4. The statement in the abstract 'ER patients and those with shorter diagnostic intervals… ' (albeit wrongly defined) …' had significantly poorer survival. Of course they will, have but not as a cause of the shorter diagnostic interval.

- This statement has been removed in the revised manuscript.

5. 'Data extracted from patient charts…' – these are open to all manner of biases (as outlined in the Weller paper above)

- We agree with this statement and have expanded on this in the limitations.

6. 'Date of suspicion' is almost impossible to define from records and has no validity as a construct.

- Date of suspicion was defined incorrectly and has been revised as date of first presentation.

7. In the analysis, many of the factors interact with each other – no attempt appears to have been made to adjust for these

- Interaction terms have now been tested, and we have found a significant interaction for the analysis in Table 4.