

Diagnostic and referral intervals for Manitoba women with epithelial ovarian cancer — the Manitoba Ovarian Cancer Outcomes (MOCO) study group: a retrospective cross-sectional study

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Abstract

Background: Epithelial ovarian cancer has the highest mortality of all gynecologic cancers. The poor survival rates are often attributed to the advanced stage at which most of these cancers are detected. We sought to examine the effects of patient demographics, comorbidities and presenting symptoms on diagnostic and referral intervals by location of first presentation (emergency department v. elsewhere) and to identify factors that affect these intervals.

Methods: We performed a retrospective analysis of chart and medical record data for ovarian cancers, with the exceptions of sex cord and germ cell tumours, diagnosed between 2004 and 2010 in Manitoba, Canada. Data were collected on baseline characteristics, time to diagnosis and referral, number and type of physician visits and emergency department visits.

Results: The final cohort consisted of 601 patients. Sixty-three percent of patients received their diagnosis within 60 days of initial presentation, and 75.2% had their cancer diagnosed within 2 physician encounters. The median diagnostic interval for all stages of patients presenting to the emergency department was 7 days, compared with 55 days for patients presenting elsewhere. Early stage patients not presenting to the emergency department had their diagnosis a median of 34.0 days later than patients with advanced disease (95% confidence interval [CI] 22.22 to 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 emergency department (odds ratio [OR] 0.40, 95% CI 0.24 to 0.64, $p = 0.0001$; OR 0.28, 95% CI 0.14 to 0.59, $p = 0.007$) than those with unclassified epithelial histotype.

Interpretation: For this group of patients, the main factor associated with diagnostic and referral intervals is presentation to the emergency department. These patients likely required more urgent attention for their more symptomatic disease, leading to quicker diagnosis and referral patterns, despite poorer prognosis.

Epithelial ovarian cancer has the highest mortality of all gynecologic cancers.¹⁻⁶ The poor survival rates for epithelial ovarian cancer are often attributed to the advanced stage at which most cases are detected.¹⁻⁸ For cases diagnosed between 2004 and 2007 in Alberta, Manitoba, and British Columbia, almost 65% were diagnosed at late stage, with age-standardized 1-year relative survival of 82.3% and 57% for stages III and IV, respectively.⁷ Common thought is that to improve the prognosis of patients with epithelial ovarian cancer, earlier detection is paramount, regardless of other characteristics.^{4,9} Delays in diagnosis and referral to a gynecologic oncologist after the point of suspicion are thought to contribute to poor survival overall.⁹

Our objective was to measure and characterize diagnostic (time from first presentation to point of diagnosis) and refer-

ral (time from first presentation to encounter with gynecologic oncologist) intervals for Manitoba patients with epithelial ovarian cancer location of first presentation (emergency department v. elsewhere), and to assess the effect of variables including patient demographics, presence of comorbidities and specific disease characteristics on the length of these intervals.

Competing interests: None declared.

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Methods

Setting/design

We developed a database encompassing cases of epithelial ovarian cancer diagnosed between Jan. 1, 2004, and Dec. 31, 2010, for a retrospective study conducted in Manitoba. Records were identified through the Manitoba Cancer Registry. The morphologies of sex cord and germ cell were excluded.

Sources of data

Data extracted from the Manitoba Cancer Registry 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 follows: type 1 (mucinous, low-grade serous, low- to moderate-grade endometrioid, clear cell) and type 2 (moderate- to 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 nonemergent basis. Administrative data from Manitoba Health (physician claims and hospital data) were used to confirm the physician encounter date where cancer was suspected. The administrative data were 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 epithelial ovarian cancer, or where there was incidental finding of epithelial ovarian cancer. Date of referral encounter was recorded as the initial appointment with a gynecologic oncologist. Because 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 the initial visit with the gynecologic oncologist.^{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 oncologist encounter and to first treatment. Predictor variables for the regression models included age, stage, histotypes, residence, income, comorbidities and symptoms at first presentation. In addition, analyses were stratified by whether first presentation was in the emergency department or elsewhere. Kaplan–Meier curves stratified by emergency

department visit and time-to-diagnosis were calculated. A logistic regression model was used to predict whether first presentation was in the emergency department or 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.

Ethics approval

Institutional research ethics board approval (HREB H2012:145) was obtained for this study.

Results

Six hundred eighty-seven patients in Manitoba received a diagnosis of epithelial ovarian cancer during the study period, but 86 patients were not referred to CancerCare Manitoba and did not have chart information, leaving a final group of 601 patients in our cohort. 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 patients had their initial diagnosis by 1 of several methods: histology ($n = 287$, 47.8%), cytology ($n = 257$, 42.8%), radiology ($n = 42$, 7.0%), serum cancer antigen 125 (CA-125) level (with clinical correlation) ($n = 14$, 2.3%). 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 received treatment based on cytology alone.

When the number of encounters was examined, 23.0%, 52.3%, 19.6%, 4.5% and 0.7% of patients received a diagnosis in 1, 2, 3, 4 and 5 encounters, respectively. Among the most frequent pathways to diagnosis, 22.0% of patients had encountered a family physician and a gynecologic oncologist, 12.5% had 1 encounter in the emergency department, 9.3% had an emergency department encounter followed by a referral to a gynecologic oncologist, 7.2% had encountered only a family physician before diagnosis and 21.0% had an interaction with an obstetrician/gynecologist during their diagnostic interval. For patients with 2 encounters, usually a family or emergency physician referred the patient to a gynecologic oncologist. In the cases with 1 encounter, typically a family or emergency physician made the diagnosis before confirmation of the diagnosis by a gynecologic oncologist. Half of the cohort was seen by a gynecologic oncologist before diagnosis (53.6%), and only 4.7% were never seen by a gynecologic oncologist.

Almost half of the study cohort received their diagnosis within 30 days of initial presentation (43.3% of all patients), and 62.6% of patients received their diagnosis within 60 days

of initial presentation (Figure 1). A total of 74.4% of all patients received their diagnosis within 90 days of presentation with signs or symptoms of epithelial ovarian cancer or after incidental findings on physical examination or imaging. Owing to the expected difference in diagnostic intervals in the emergency department compared with other settings, analyses for diagnostic, referral and treatment intervals were stratified by emergency department status at first presentation. Significant differences in diagnostic, referral and treatment intervals were seen between emergency department and non-emergency department patients. The median diagnostic interval for a patient in the emergency department was 7 days, compared with 55 days for patients elsewhere (Figure 1; $p < 0.0001$). The median referral interval for patients in the emergency department was 18 days, compared with 56 days for patients elsewhere (Figure 2; $p = 0.0063$). Time from first presentation to first treatment was very highly correlated with time from first presentation to diagnosis ($r > 0.95$; Appendix 1, available at www.cmajopen.ca/content/5/1/E116/suppl/DC1). Therefore, the treatment interval as an outcome was not investigated further.

To extend our analyses, we further evaluated the emergency department and non-emergency department populations to identify predictors related to diagnostic and referral intervals; for univariable analyses, see Appendices 2–5 (available at www.cmajopen.ca/content/5/1/E116/suppl/DC1), and for multivariable analyses see Table 2 and Table 3. However, most predictors as outlined in Table 1 were not statistically significant after multivariable analysis.

Survival was assessed to determine the impact of emergency department status and diagnostic interval (Figure 3). Patients in the emergency department and patients with shorter diagnostic interval had significantly poorer survival. Predictors of emergency department presentation were also assessed (for univariable analyses see Appendix 6, available at www.cmajopen.ca/content/5/1/E116/suppl/DC1, and for multivariable analyses see Table 4). The odds of a patient who presented in the emergency department having unclassified disease were higher than that for a non-emergency department patient. In addition, patients with high or very high comorbidity and patients with abdominal pain were more likely to first present in the emergency department (high comorbidity odds ratio [OR] 3.028, 95% confidence interval [CI] 1.73 to 5.29, $p = 0.0001$; very high comorbidity OR 4.149, 95% CI 2.44 to 7.07, $p < 0.0001$), with a significant interaction between the 2 factors (OR 0.396, 95% CI 0.17 to 0.91, $p = 0.03$), suggesting that the effect of abdominal pain decreased if the patient had high or very high comorbidity. Urban residents were more likely to present to the emergency department than rural patients were (OR 2.421, 95% CI 1.60 to 3.67, $p < 0.0001$).

Interpretation

Most patients with epithelial ovarian cancer in Manitoba from 2004 to 2010 received their diagnosis within 2 encounters and 60 days of their initial presentation. Among non-emergency

department patients, presentation at an earlier stage and without substantial comorbidity was associated with longer diagnostic intervals. Therefore, relatively healthy patients who present with less severe symptoms likely have less urgent investigations. Patients who presented to the emergency department were more likely to have more severe disease,

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

Characteristic	First presentation in the ED, no. (%) [*]	
	No n = 430	Yes n = 171
Age, yr, mean ± SD	62.7 ± 13.7	65.2 ± 16.1
Stage		
I	114 (26.5)	23 (13.5)
II	56 (13.0)	17 (10.0)
III	143 (33.3)	57 (33.3)
IV	73 (17.0)	47 (27.5)
Unknown	44 (10.2)	27 (15.8)
Histotype		
Serous	175 (40.7)	48 (28.1)
Unclassified	100 (23.3)	69 (40.3)
Clear cell	29 (6.7)	7 (4.1)
Endometrioid	41 (9.5)	< 6 (< 4.0)
Mucinous	37 (8.6)	11 (6.4)
Other	48 (11.2)	31 (18.1)
Type		
I	96 (22.3)	24 (14.0)
II	334 (77.7)	147 (86.0)
Residence		
Urban	226 (52.6)	119 (69.6)
Rural	204 (47.4)	52 (30.4)
Income		
Rural 1–Rural 3	112 (26.0)	25 (14.6)
Rural 4–Rural 5	73 (17.0)	20 (11.7)
Urban 1–Urban 3	148 (34.4)	88 (51.5)
Urban 4–Urban 5	92 (21.4)	32 (18.7)
Missing	< 6 (< 4.0)	< 6 (< 4.0)
Comorbidity		
Low	19 (4.4)	< 6 (< 4.0)
Resource utilization band		
Moderate	287 (66.7)	91 (53.2)
High	89 (20.7)	46 (26.9)
Very high	35 (8.1)	28 (16.4)
Abdominal pain	144 (33.5)	91 (53.2)
Abdominal distension	118 (27.4)	61 (35.7)
Incidental	58 (13.5)	9 (5.3)
Bowel symptoms	36 (8.4)	20 (11.7)
Nausea	24 (5.6)	19 (11.1)
Decreased appetite	31 (7.7)	11 (6.4)
Respiratory symptoms	17 (3.9)	22 (12.9)
Weight change	26 (6.0)	10 (5.8)
Urinary symptoms	24 (5.6)	5 (2.9)
Abnormal bleeding	28 (6.5)	2 (1.2)
Postmenopausal bleeding	29 (6.7)	1 (0.6)
Palpable mass	22 (5.1)	4 (2.3)
Weakness	14 (3.3)	11 (6.4)
Emesis	12 (2.8)	12 (7.0)

Note: ED = emergency department, SD = standard deviation.
^{*}Unless otherwise specified

more often showed abdominal and respiratory symptoms, and likely prompted more aggressive investigations, which led to shorter diagnostic and referral intervals. The diagnostic intervals were shorter than referral intervals, which suggests other physicians diagnosing epithelial ovarian cancer before referral to subspecialists. These factors likely explain why patients who presented to the emergency department had poorer sur-

vival than those who presented elsewhere. Our data show that most patients receive a diagnosis within 60 days after 2 health care encounters after initial presentation; only 5.2% of patients required 4 or more physician encounters before diagnosis. In addition, we examined diagnostic interval, referral interval and treatment interval and found that they were highly correlated.

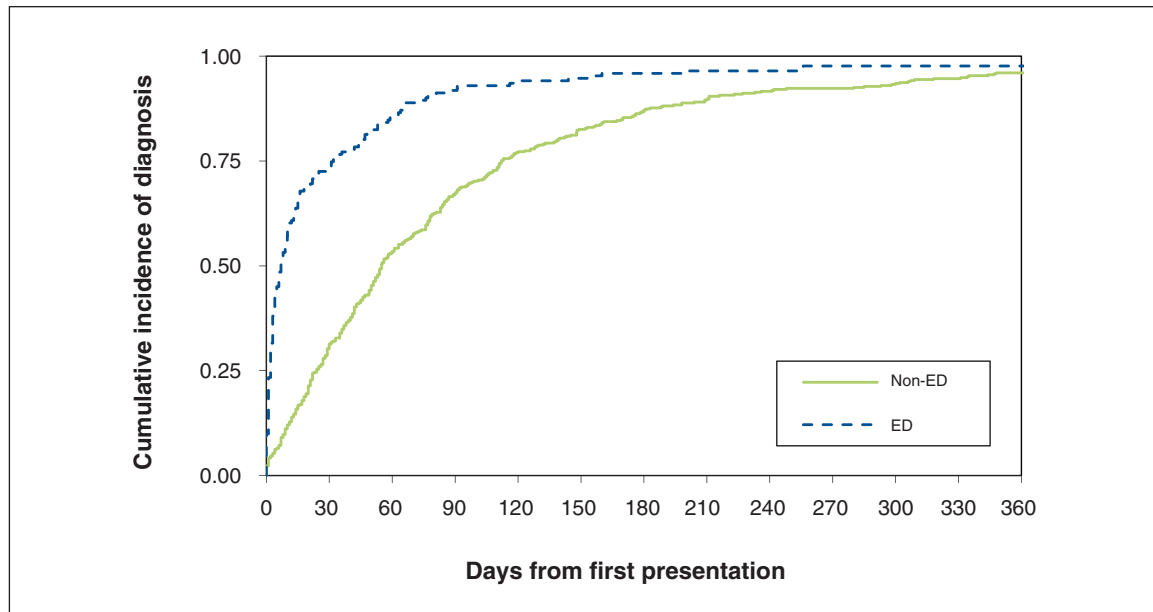


Figure 1: Cumulative incidence of diagnosis for patients with epithelial ovarian cancer who presented to the emergency department (ED) or elsewhere (Non-ED). Incidence of diagnosis was measured over time (days) from point of initial presentation. Patients presenting in the emergency department received their diagnoses sooner than those presenting elsewhere.

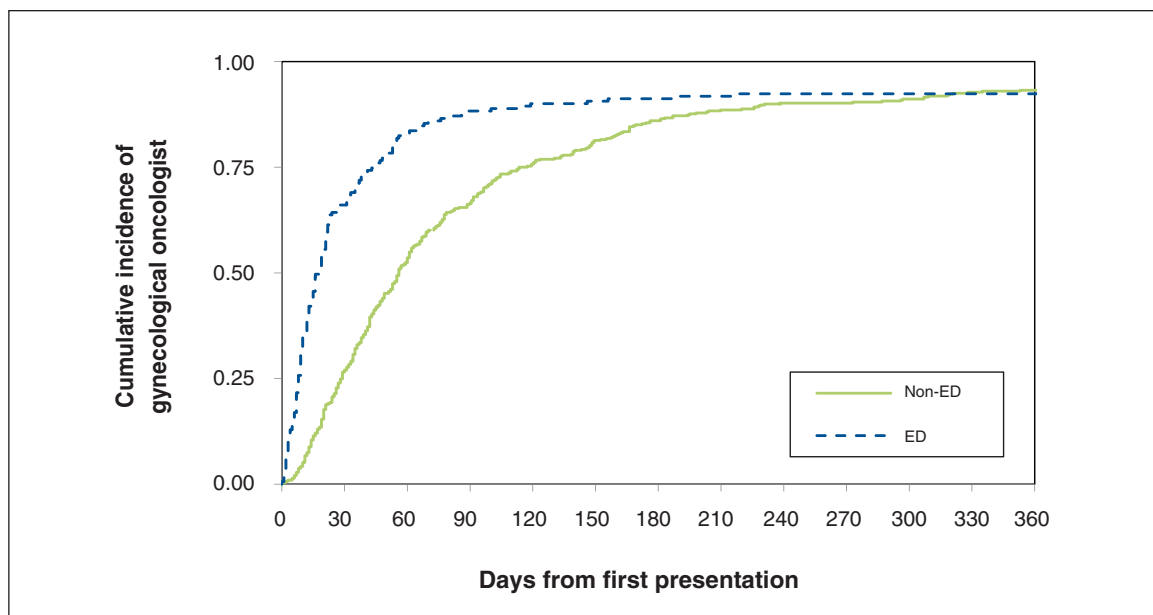


Figure 2: Cumulative incidence of gynecological oncologist encounters for patients with epithelial ovarian cancer who presented to the emergency department (ED) or elsewhere (Non-ED). Incidence of referral was measured over time (days) from point of presentation. Similar to incidence of diagnosis, patients who presented to the emergency department were referred sooner than those presenting elsewhere.

One survey study found a median interval of 37 days from symptom onset to diagnosis,¹⁴ which is comparable with our results. Theoretically, faster diagnosis in the primary care setting would lead to detection at an earlier stage; however, the present study also found that initial presentation in the emergency department and having a shorter diagnostic interval are related to poorer survival. Similarly, in a study involving a cohort of adolescents and young adults with cancer, Xu and colleagues identified that having a first contact through a visit to the emergency department was related to lower survival, but that delays in the diagnostic interval or treatment were not related to outcome.¹⁵ Moreover, data from Nagle and colleagues suggest that a longer diagnostic interval for symptomatic women with invasive epithelial ovarian cancer does not adversely affect survival,¹⁶ and Robinson and colleagues found that increased pain scores were associated with worsened survival.¹⁷ Both studies were based on patient questionnaires and therefore open to recall bias. Kirwan and colleagues showed how survival was related to patient age and stage at diagnosis, but that delays in patient reporting and referral from primary care were not related to survival.¹⁸ This was also supported by Menczer and colleagues, 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 emergency department.

Multiple studies have examined screening and early detection and shown that there is no benefit to overall survival. Gilbert and colleagues trialed open-access CA-125 and ultrasonography testing for women with symptoms of epithelial ovarian cancer. The late-stage cases that were detected had smaller, more resectable tumour volumes, with a larger pro-

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

Variable	Median difference (95% CI)
Presentation beginning in the ED	
(Intercept)	23.96 (3.01 to 44.90)
Abdominal pain and emesis	
Pain and no emesis	7.04 (2.26 to 11.83)
Pain and emesis	-1 (-10.50 to 8.50)
No pain or emesis	(reference)
Type	
II	-20.96 (-41.88 to -0.03)
I	(reference)
Presentation beginning elsewhere	
(Intercept)	52.04 (43.47 to 60.61)
Stage	
I/II	33.96 (22.22 to 45.69)
III/IV	(reference)
Unknown	2.00 (-16.26 to 20.26)
Abdominal distension	
Yes	-28.04 (-38.00 to -18.08)
No	(reference)
Postmenopausal bleeding	
Yes	56.00 (18.77 to 93.23)
No	(reference)

Note: CI = confidence interval, ED = emergency department.

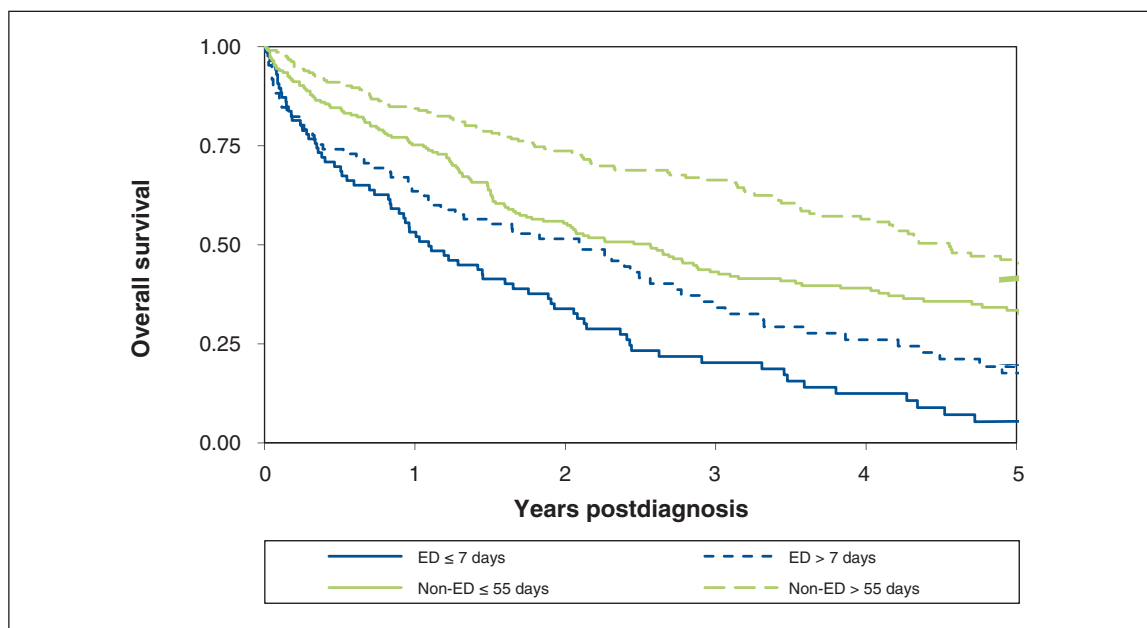


Figure 3: Kaplan–Meier curve showing overall survival for patients with epithelial ovarian cancer who presented to the emergency department (ED) or elsewhere (Non-ED). Patients who presented to the emergency department showed poorer survival than those who presented elsewhere.

Table 3: Multivariable quantile regression models predicting referral intervals (in days) by emergency department status at initial presentation

Variable	Median difference (95% CI)
Presentation beginning in the ED	
(Intercept)	19.00 (14.32 to 23.68)
Abdominal distension	
Yes	-7.00 (-13.16 to -0.84)
No	(reference)
Presentation beginning elsewhere	
(Intercept)	68.96 (59.03 to 78.89)
Comorbidities	
High/very high	-16.96 (-27.53 to -6.39)
(Resource utilization band)	
Moderate and lower	(reference)
Abdominal distension	
Yes	-28.92 (-39.95 to -17.88)
No	(reference)

Note: CI = confidence interval, ED = emergency department.

portion 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 with 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, which shows that most patients receive a diagnosis within 90 days of presentation and that the diagnostic, referral and treatment intervals are all closely related.

Strengths and limitations

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 and colleagues.¹³ These timelines were not based on questionnaires, thus avoiding patient recall bias.¹³

Some analyses might have been underpowered, particularly in calculating the effect of variables within the smaller emergency department patient population. In addition, all relevant information may not have been recorded in the patient charts (e.g., all symptoms at all visits). Although we avoided recall bias using this method, gathering the date of first presentation from patient records may not represent the “true” start of patient symptoms; the patient may have presented to the health care system with other “charted” conditions, yet still suffered from the symptoms under question. It is unknown how long patients

Table 4: Multivariable logistic regression model predicting patients who appear in the emergency department at first suspicion versus elsewhere

Variable	OR (95% CI)
Morphology	
Serous carcinoma	0.39 (0.24 to 0.64)
Unclassified epithelial	1.00
Clear cell/endometrioid	0.28 (0.13 to 0.59)
Mucinous	0.52 (0.23 to 1.15)
Other*	0.91 (0.50 to 1.65)
Residence	
Winnipeg	2.42 (1.60 to 3.67)
Non-Winnipeg	1.00
Comorbidities	
High/very high	3.03 (1.73 to 5.29)
(Resource utilization band)	
Moderate and lower	1.00
Abdominal pain	
Yes	4.15 (2.44 to 7.07)
No	1.00
Respiratory symptoms	
Yes	4.98 (2.32 to 10.70)
No	1.00
Abnormal bleeding	
Yes	0.21 (0.05 to 0.94)
No	1.00
Postmenopausal bleeding	
Yes	0.12 (0.02 to 0.93)
No	1.00
Interaction between comorbidities and abdominal pain	
	0.40 (0.17 to 0.91)

Note: CI = confidence interval, ED = emergency department, OR = odds ratio.
*Other epithelial-stromal, and miscellaneous and unspecified.

had symptoms before initial presentation; however according to Tokuda and colleagues, ovarian cancer has a symptom interval median of 15 days and mean of 38.5 days.²³

Conclusion

Our study has identified that the main factor associated with the diagnostic interval in epithelial ovarian cancer is the setting of the initial presentation (emergency department v. elsewhere). Patients who presented to the emergency department were more likely to have abdominal pain and respiratory symptoms, and possibly more aggressive disease. They were likely more quickly investigated, leading to quicker diagnosis and referral, despite poorer prognosis. By contrast, women presenting in the community with nonspecific symptoms more often had considerably longer diagnostic and referral intervals, but better out-

comes. Although it is important to emphasize awareness and early detection of epithelial ovarian cancer by primary care practitioners in the community, improving the prognosis for this condition is a complex, evolving algorithm. One factor for detection to be considered is the availability of primary care providers. In our cohort, it is possible that patients who presented to the emergency department 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 these patients without a regular primary care provider and if there is an association with disease outcomes. The Manitoba Ovarian Cancer Outcomes study group is further investigating treatment algorithms, primary care availability and adjuvant therapies to determine effects on outcomes in patients with epithelial ovarian cancer.

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