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Prehospital care for ovarian cancer in Catalonia: could we do better in primary care? Retrospective cohort study

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ABSTRACT

Objective To assess the impact of prehospital factors (diagnostic pathways, first presentation to healthcare services, intervals, participation in primary care) on 1-year and 5-year survival in people with epithelial ovarian cancer (EOC).

Design Retrospective quasi-population-based cohort study.

Setting Catalan Integrated Public Healthcare System.

Participants People with EOC who underwent surgery with a curative intent in public Catalan hospitals between 1 January 2013 and 31 December 2014.

Outcome measures Data from primary and secondary care clinical histories and care processes in the 18 months leading up to confirmation (signs and symptoms at presentation, diagnosis pathways, referrals, diagnosis interval) of the EOC diagnosis (stage, histology type, treatment). Diagnostic process intervals were based on the Aarhus statement. 1-year and 5-year survival analysis was undertaken.

Results Of the 513 patients included in the cohort, 67.2% initially consulted their family physician, while 36.4% were diagnosed through emergency services. In the Cox models, survival was influenced by advanced stage at 1 year (HR 3.84, 95% CI 1.23 to 12.02) and 5 years (HR 5.36, 95% CI 3.07 to 9.36), as was the type of treatment received, although this association was attenuated over follow-up. Age became significant at 5 years of follow-up. After adjusting for age, adjusted morbidity groups, stage at diagnosis and treatment, 5-year survival was better in patients presenting with gynaecological bleeding (HR 0.35, 95% CI 0.16 to 0.79). Survival was not associated with a starting point involving primary care (HR 1.39, 95% CI 0.93 to 2.09), diagnostic pathways involving referral to elective gynaecological care from non-general practitioners (HR 0.80, 95% CI 0.51 to 1.26), or self-presentation to emergency services (HR 0.82, 95% CI 0.52 to 1.31).

Conclusions Survival in EOC is not associated with diagnostic pathways or prehospital healthcare, but it is influenced by stage at diagnosis, administration of primary cytoreduction plus chemotherapy and patient age.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The main strength is that this is one of the few studies to investigate the relationship between the prehospital diagnostic pathway for ovarian cancer and 1-year and 5-year survival.
⇒ Four data sources were used, including hospital and primary care clinical records, which enabled a detailed understanding of the patient profile in the 18 months prior to diagnostic confirmation.
⇒ Limitations include its retrospective nature, exclusion of borderline tumours, other tumours that were not treated with surgery with a curative intent, and tumours treated in private hospitals.

INTRODUCTION

Ovarian cancer, encompassing fallopian tube cancer and peritoneal cancer, is the eighth most common cancer, the fifth most lethal,[1] and the gynaecological cancer with the worst survival.[2] One-year and 5-year survival varies widely in different European countries,[2–4] but 5-year survival rates have barely changed over the past several decades, remaining under 45% in most countries[4 5] and about 39.8% (95% CI 36.9% to 42.7%) in Spain.[4]

Survival is one of the key indicators of the accessibility and quality of healthcare services in patients with cancer,[4] and it is influenced by the healthcare model in each country.[6] At the same time, survival rates vary according to age, ethnicity, stage at diagnosis and histology[7] as well as health status (comorbidities) prior to diagnosis and treatment response.

One-year survival is strongly influenced by the diagnostic pathway in cancer.[8] For all neoplasms, this indicator is significantly lower for cases diagnosed in emergency services compared with any other diagnostic setting,[8] even after adjusting for age and stage at diagnosis.[9 10] Relatively low 1-year survival rates are considered to indicate more advanced disease at the time of diagnosis, which could reflect the biology of the tumour (aggressive tumour growth) but also the time to diagnosis.[11] The diagnostic interval, regardless of its impact on survival, is a reference indicator for quality cancer care.

Health systems in which primary healthcare acts as the gatekeeper to the rest of the

system are associated with worse 1-year survival in cancer,[6] possibly due to more prolonged diagnostic intervals. Diagnosis can be delayed due to difficulties recognising non-specific initial symptoms as potentially malignant and/or suboptimal access to complementary diagnostic tests.[12]

The aim of this study is to assess the influence of prehospital healthcare factors (diagnostic pathways, characteristics of first presentation to healthcare services, intervals, participation in primary care) on 1-year and 5-year survival in women with epithelial ovarian cancer (EOC), treated surgically with a curative intent in public Catalan hospitals in 2013 and 2014.

MATERIALS AND METHODS

Study design

Retrospective quasi-population-based cohort study of EOC in the Catalan Integrated Public Healthcare System.

Participants and study period

The study includes all patients treated surgically with a curative intent for EOC for the first time in public hospitals between 1 January 2013 and 31 December 2014. Patients were identified based on the primary diagnostic and procedural codes recorded in electronic hospital registries. We excluded cases treated for a recurrence, unresectable tumours and/or surgeries with a palliative intent. The public health system in Spain is based on a national health service model.

Patient and public involvement

Four data sources were used: audit of the hospital clinical histories, undertaken within the framework of the Catalan cancer plan in 2016; audit of clinical histories in primary care, performed in 2018; adjusted morbidity groups (AMGs); and the Catalan Insurance Registry. Patients and public were not involved during the research.

Data from the hospital audit include information on patient age, date and stage at diagnosis, histology and type of treatment and surgery. Moreover, follow-up data were collected for recurrences, disease progression and death.

Using a purpose-designed questionnaire, two family physicians (CV-V and MM-C) collected data from primary care clinical histories and care processes in the 18 months leading up to confirmation of the cancer diagnosis, including: patient-reported date of symptoms onset; date of first consultation with a healthcare professional; signs and symptoms at presentation; number and dates of successive visits to different professionals; diagnostic tests and referrals ordered; and reason justifying the suspicion of ovarian cancer. Moreover, they recorded personal and family history of cancer (ovarian, breast, colorectal). Duplicate extractions were carried out in case of doubt, and disagreements were resolved by consensus. A description of the variables and categories used is provided in online supplemental information S1.

Diagnostic pathways are classified according to the care level where the suspicion of malignancy first arose and the referral pathway,[8] in our case to the gynaecology/oncogynecology service in the reference hospital. Five diagnostic pathways were defined: (A) self-presentation to the emergency department (ED); (B) referral to the ED from family physician; (C) referral to elective gynaecology/oncogynecology care from family physician; (D) referral to elective gynaecology/oncogynecology care from specialist other than family medicine and (E) other (eg, private healthcare, referral from another Spanish region). Information was collected from administrative records, following contextual criteria.[9 11]

Data collection, analysis of time points, and calculation of the diagnostic process intervals are based on the Aarhus statement.[13] Time points of interest were defined as the date of: first symptom; first visit to healthcare services; suspicion of ovarian cancer (referral to gynaecology/oncogynecology service at the reference hospital); diagnostic confirmation, considering diagnostic procedures performed (cytology, histology, imaging) according to the hierarchical criteria recommended by the International Agency for Research Cancer [14]; and the first treatment received (surgery or neoadjuvant treatment).

Comorbidity was assessed using AMGs, which are calculated systematically from information in the healthcare records, according to the level of risk at the time of suspicion of ovarian cancer but prior to its diagnosis.[15]

Signs and symptoms at first presentation were divided into four categories: unspecific symptoms, gynaecological symptoms, signs associated with advanced ovarian cancer, and asymptomatic.[16 17]

Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.[18]

Statistical analysis

We performed a descriptive analysis of all variables according to five diagnostic pathways, expressing categorical variables as absolute and relative frequencies and continuous variables as measures of central tendency and dispersion. The association between categorical variables and diagnostic pathways was calculated using the χ^2 test. A post hoc paired comparison analysis was performed using the Z test with Bonferroni's correction. In the analysis of continuous variables, we used the analysis of variance test for independent samples or the non-parametric Kruskal-Wallis test. The Cox proportional hazards model was used for univariate and multivariate regression analyses of 1-year and 5-year survival. For the survival analysis, the length of follow-up was calculated from the date of diagnostic confirmation to death from any cause, censor or study end (October 2020). Type I errors were established at 5%. The statistical analysis was performed with SPSS software (V.21).

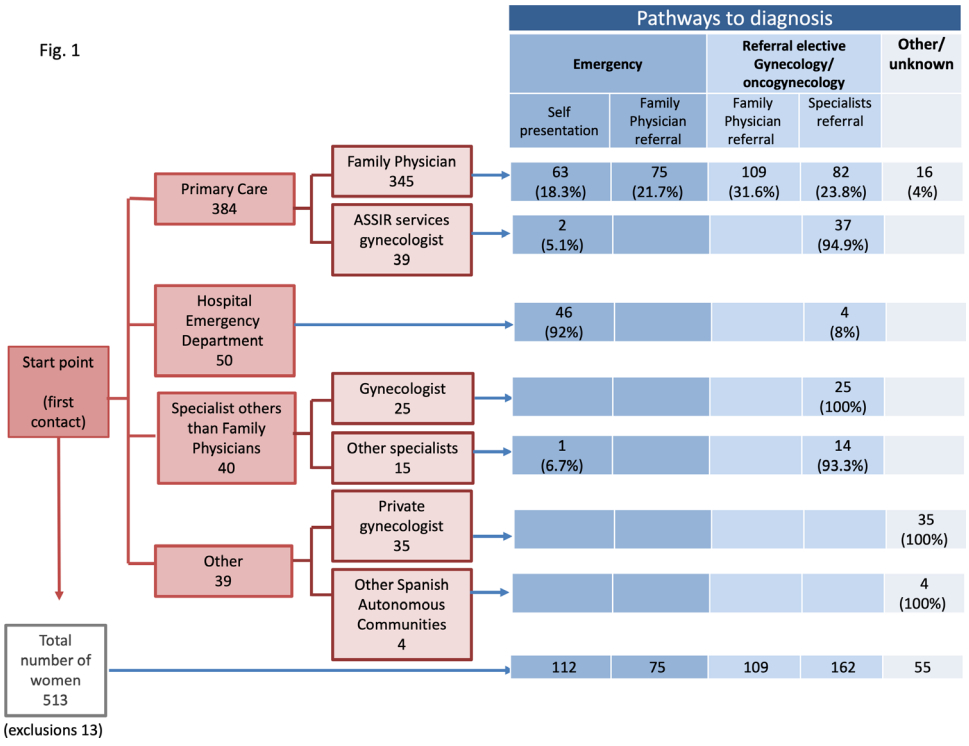

Figure 1 First contact with the healthcare system and the pathway followed to the oncogynecology service. ASSIR, sexual health and reproductive care centres.

RESULTS

The cohort included 513 women with ovarian cancer, over half of whom were managed through elective healthcare (figure 1). Patients' first contact with the healthcare system was through their family physician in approximately two out of every three cases (figure 1).

Self-presentation to emergency services was associated with the highest proportion of cancers diagnosed at an advanced stage and with interval surgery and neoadjuvant chemotherapy (table 1). Primary care referrals to the ED show a similar pattern, although to a slightly lesser extent. Patients self-presenting to emergency services were also somewhat younger, presented more high-grade serous carcinomas and consequently a greater proportion of tumours with type II histology compared with patients diagnosed through other pathways; however, these differences were not statistically significant.

Among the 89.3% of the women who were symptomatic, the most frequent initial signs and/or symptoms were abdominal pain (46.4%), followed by abdominal distension (15.0%) and vaginal bleeding (14.4%) (table 2). Abdominal distension was significantly more common in people self-presenting to emergency services compared with other diagnostic pathways, while abdominal pain was reported most frequently in those self-presenting to emergency services and to elective primary care. Vaginal bleeding was reported most frequently in elective primary care. Overall, emergency pathways, both self-presentations and referrals, were most closely associated with signs of advanced disease. Asymptomatic patients were mostly diagnosed through elective care from specialists other than family physicians.

The entry point to the healthcare system was primary care (either family medicine or sexual and reproductive health services) in 74.9% of the patients. The median number of visits to family medicine before diagnosis was 6, but this number was higher in the cases of the emergency pathways (seven visits) and elective family medicine (eight visits). Over one-third of the women (35.7%), most of whom were diagnosed after self-presentation to the ED, were referred directly to the gynaecology/oncogynecology service following the initial visit; 22.8%, mostly diagnosed in the ED following a primary care referral, had had two or more previous referrals.

The most frequent reason justifying a referral to the gynaecology/oncogynecology service, in 64.3% of the cases, was a suspicious imaging test, with significant differences in the proportion of patients referred for this reason in emergency self-presentations versus emergency referrals. Ten per cent of the cases were referred following histological findings of epithelial ovarian carcinoma on a surgical specimen taken for another reason.

Among the 458 symptomatic women, the median diagnostic interval was 110.5 days, and it was under 60 days in 34.9% of the cases (table 3). The diagnostic interval, the interval to the last referral, and the treatment interval were shorter in the emergency self-presentation pathway than in the pathway involving elective care from a specialist other than a family physician. The intervals

Table 1 Ovarian cancer patient profile and tumour characteristics by diagnostic pathway

	Diagnostic pathway												
	Self-presentation to ED (N=112)		Family physician referral to ED (N=75)		Referral to elective gynaecology/ oncogynecology from family physician (N=109)		Referral to elective gynaecology/ oncogynecology care from other specialist (N=162)		Other/unknown (N=55)		TOTAL (N=513)		
Variables	n	%	n	%	n	%	n	%	n	%	n	%	P value*
Age (years)													
Mean (SD)	59.5 (12.6)		59.8 (13.2)		60.2 (12.9)		60.8 (12.1)		58.8 (13.6)		60.0 (12.7)		0.86†
Median (IQR)	59.5 (19.0)		60.0 (21.0)		60.0 (16.0)		61.0 (16.0)		61.0 (19.0)		60.0 (18.0)		
<50	18	16.1	16	21.3	22	20.2	29	17.9	13	23.6	98	19.1	0.91
50–59	38	33.9	20	26.7	31	28.4	43	26.5	12	21.8	144	28.1	
60–69	30	26.8	17	22.7	31	28.4	50	30.9	16	29.1	144	28.1	
≥70	26	23.2	22	29.3	25	22.9	40	24.7	14	25.5	127	24.8	
Comorbidity. AMG health risk grades													
No comorbidity	33	29.5	14	18.7	16	14.7	22	13.6	13	23.6	98	19.1	0.014‡
Moderate (1 system)	11	9.8	9	12	19	17.4	36	22.2	14	25.5	89	17.3	
High (2–3 systems)	44	39.3	27	36	39	35.8	58	35.8	14	25.5	182	35.5	
Very high (+3 systems)	24	21.4	25	33.3	35	32.1	46	28.4	14	25.5	144	28.1	
Stage													
I-II	21	18.8	25	33.3	42	38.5	62	38.3	17	30.9	167	32.6	0.007‡
III-IV	91	81.3	50	66.7	67	61.5	100	61.7	38	69.1	346	67.4	
Histological type													
High-grade serous	81	72.3	50	66.7	66	60.6	103	63.6	35	63.6	335	65.3	0.55
Low grade serous	2	1.8	3	4	2	1.8	3	1.9	3	5.5	13	2.5	
Mucinous	4	3.6	4	5.3	10	9.2	6	3.7	3	5.5	27	5.3	
Endometrioid	11	9.8	6	8	15	13.8	23	14.2	7	12.7	62	12.1	
Clear cell	6	5.4	8	10.7	13	11.9	21	13	5	9.1	53	10.3	
Undifferentiated/other epithelial	8	7.1	4	5.3	3	2.8	6	3.7	2	3.6	23	4.5	
Histological group													
Type I	27	24.1	24	32	43	39.4	58	35.8	18	32.7	170	33.1	0.16
Type II	85	75.9	51	68	66	60.6	104	64.2	37	67.3	343	66.9	
Treatment													
Only surgery	9	8	10	13.3	17	15.6	17	10.5	5	9.1	58	11.3	0.001‡
Neoadjuvant therapy+surgery	6	5.4	5	6.7	4	3.7	5	3.1	3	5.5	23	4.5	
Surgery+adjuvant therapy	41	36.6	28	37.3	56	51.4	102	63	27	49.1	254	49.5	

Continued

Table 1 Continued

Variables	Diagnostic pathway												
	Self-presentation to ED (N=112)		Family physician referral to ED (N=75)		Referral to elective gynaecology/ oncogynecology from family physician (N=109)		Referral to elective gynaecology/ oncogynecology care from other specialist (N=162)		Other/unknown (N=55)		TOTAL (N=513)		
	n	%	n	%	n	%	n	%	n	%	n	%	P value*
Neoadjuvant therapy+surgery + adjuvant therapy	56	50	32	42.7	32	29.4	38	23.5	20	36.4	178	34.7	
Type of surgery													
Surgical staging (EI-II)	21	18.8	24	32	43	39.4	62	38.3	17	30.9	167	32.6	0.001‡
Primary debulking surgery (EIII-IV)	29	25.9	14	18.7	31	28.4	58	35.8	16	29.1	148	28.8	
Interval debulking surgery (EIII-IV)	62	55.4	37	49.3	35	32.1	42	25.9	22	40	198	38.6	
Family history of cancer													
Ovarian cancer	5	4.5	4	5.3	5	4.6	7	4.3	2	3.6	23	4.5	0.99
Breast cancer	16	14.3	8	10.7	8	7.3	21	13	3	5.5	56	10.9	0.27
Colorectal cancer	2	1.8	6	8	4	3.7	6	3.7	3	5.5	21	4.1	0.31
More than one of these cancers	22	19.6	17	22.7	22	20.2	40	24.7	13	23.6	114	22.2	0.86
Unknown cancer	4	3.6	1	1.3	7	6.4	12	7.4	5	9.1	29	5.7	0.21
Personal history of cancer													
Breast cancer	8	7.1	4	5.3	4	3.7	21	13	3	5.5	40	7.8	0.045
Colorectal cancer	2	1.8	1	1.3	1	0.9	6	3.7	1	1.8	11	2.1	0.56
More than one of these cancers	12	10.7	9	12	13	11.9	34	21	10	18.2	78	15.2	0.098
Unknown cancer	2	1.8	4	5.3	8	7.3	9	5.6	6	10.9	29	5.7	0.16

*P value: $\chi 2$ test.
†One-factor ANOVA.
‡Statistical significance ($p<0.05$).
AMG, adjusted morbidity groups; ANOVA, analysis of variance; ED, emergency department.;

Table 2 Description of prehospital care factors

Variables	Diagnostic pathways										Total (N=513)		P value*
	Self-presentation to ED (N=112)		Family physician referral to ED (N=75)		Referral to elective gynaecology/ oncogynecology from family physician (N=109)		Referral to elective gynaecology/ oncogynecology care from other specialist (N=162)		Other/unknown (N=55)				
	n	%	n	%	n	%	n	%	n	%	n	%	
Presenting symptom													
Pelvic/abdominal pain/ discomfort	62	55.4	36	48.0	60	55.0	55	34.0	25	45.5	238	46.4	0.002†
Change in appetite/feeling full	8	7.1	3	4.0	4	3.7	2	1.2	2	3.6	19	3.7	0.17
Abdominal distension/bloating	34	30.4	9	12.0	12	11.0	15	9.3	7	12.7	77	15.0	<0.001†
Urinary frequency/urgency	15	13.4	10	13.3	19	17.4	18	11.1	6	10.9	68	13.3	0.63
Change in bowel movements (constipation/diarrhoea)	24	21.4	11	14.7	15	13.8	16	9.9	6	10.9	72	14.0	0.096
Back pain	14	12.5	13	17.3	15	13.8	26	16.0	4	7.3	72	14.0	0.47
Other	1	0.9	1	1.3	0	0.0	1	0.6	0	0.0	3	0.6	0.76
Presenting signs													
Ascites	10	8.9	4	5.3	0	0.0	3	1.9	3	5.5	20	3.9	0.006†
Pelvic/abdominal mass	11	9.8	4	5.3	13	11.9	12	7.4	8	14.5	48	9.4	0.31
Pleural effusion	5	4.5	6	8.0	0	0.0	0	0.0	0	0.0	11	2.1	<0.001†
Umbilical nodule/abdominal mass	2	1.8	3	4.0	1	0.9	2	1.2	1	1.8	9	1.8	0.58
Asthenia, anorexia, weight loss	7	6.3	7	9.3	4	3.7	8	4.9	2	3.6	28	5.5	0.49
Deep vein thrombosis	3	2.7	3	4.0	1	0.9	0	0.0	0	0.0	7	1.4	0.076
Lymphadenopathies	0	0.0	0	0.0	2	1.8	1	0.6	0	0.0	3	0.6	0.36
Vaginal abnormal bleeding	14	12.5	6	8.0	24	22.0	26	16.0	4	7.3	74	14.4	0.032†
Other	15	13.4	19	25.3	8	7.3	11	6.8	3	5.5	56	10.9	0.001†
Asymptomatic	1	0.9	0	0.0	3	2.8	41	25.3	10	18.2	55	10.7	<0.001†
Symptomatic profiles													
Nonspecific symptoms	66	58.9	44	58.7	62	56.9	74	45.7	28	50.9	274	53.4	<0.001†
Gynaecological symptoms (vaginal bleeding)	13	11.6	6	8.0	23	21.1	24	14.8	4	7.3	70	13.6	
Signs associated with advanced disease	32	28.6	25	33.3	21	19.3	23	14.2	13	23.6	114	22.2	
Asymptomatic	1	0.9	0	0.0	3	2.8	41	25.3	10	18.2	55	10.7	
Start point (first consultation)													
Primary care	65	58.0	75	100.0	109	100.0	119	73.5	16	29.1	384	74.9	<0.001†

Continued

Table 2 Continued

Variables	Diagnostic pathways												
	Self-presentation to ED (N=112)		Family physician referral to ED (N=75)		Referral to elective gynaecology/ oncogynecology from family physician (N=109)		Referral to elective gynaecology/ oncogynecology care from other specialist (N=162)		Other/unknown (N=55)		Total (N=513)		
	n	%	n	%	n	%	n	%	n	%	n	%	P value*
Other	47	42.0	0	0.0	0	0.0	43	26.5	39	70.9	129	25.1	
Reason for referral													
Physical examination: ascites	28	25.0	15	20.0	5	4.6	6	3.7	15	27.3	69	13.5	<0.001†
Physical examination: pelvic mass	22	19.6	14	18.7	18	16.5	16	9.9	7	12.7	77	15.0	0.17
Imaging technique	78	69.6	36	48.0	73	67.0	107	66.0	36	65.5	330	64.3	0.031†
Tumour marker	5	4.5	6	8.0	9	8.3	14	8.6	9	16.4	43	8.4	0.15
Pathological anatomy and cytology	3	2.7	11	14.7	6	5.5	28	17.3	7	12.7	55	10.7	<0.001†
Professional making the referral to gynaecologist/oncogynecologist													
Family physician	1	0.9	18	24.0	64	58.7	5	3.1	0	0.0	88	17.2	<0.001†
Emergency physician	94	83.9	33	44.0	0	0.0	4	2.5	3	5.5	134	26.1	
ASSIR services gynaecologist	0	0.0	0	0.0	31	28.4	47	29.0	0	0.0	78	15.2	
Hospital gynaecologist	3	2.7	1	1.3	11	10.1	47	29.0	5	9.1	67	13.1	
Other specialists	14	12.5	23	30.7	1	0.9	59	36.4	0	0.0	97	18.9	
Outside the public system	0	0.0	0	0.0	2	1.8	0	0.0	47	85.5	49	9.6	
No of referrals (not including referrals to gynaecologist/oncogynecologist)													
0	57	50.9	0	0.0	32	29.4	63	38.9	31	56.4	183	35.7	<0.001†
1	40	35.7	34	45.3	49	45.0	70	43.2	20	36.4	213	41.5	
2	14	12.5	25	33.3	20	18.3	24	14.8	3	5.5	86	16.8	
≥3	1	0.9	16	21.3	8	7.3	5	3.1	1	1.8	31	6.0	
Visits to family medicine§													
N, mean (SD)	6.3 (6.3)		9.1 (7.6)		10.2 (8.1)		7.0 (8.0)		5.1 (5.8)		7.6 (7.6)		<0.001†‡
Median (IQR)	5.0 (10.0)		7.0 (8.0)		8.0 (12.0)		5.0 (9.0)		3.0 (6.0)		6.0 (9.0)		
Emergency visits§													
N, mean (SD)	1.1 (1.3)		0.9 (1.1)		0.8 (3.0)		0.6 (1.2)		0.6 (1.5)		0.8 (1.8)		<0.001†‡
Median (IQR)	1.0 (2.0)		1.0 (1.0)		0.0 (1.0)		0.0 (1.0)		0.0 (1.0)		0.0 (1.0)		

*P value: χ^2 test.
†Statistical significance (p<0.05).
‡Kruskal-Wallis test
§In the last 18 months
.ASSIR, sexual health and reproductive care centres; ED, emergency department.

Table 3 Time intervals (days) for each diagnostic route

	Diagnostic pathway												
	Self-presentation to ED		Family physician referral to ED		Referral to elective gynaecology/oncogynecology from family physician		Referral to elective gynaecology/oncogynecology care from other specialist		Other/unknown		Total		
Intervals*	n	%	n	%	n	%	n	%	n	%	n	%	P value†
Symptomatic patients	N=111		N=75		N=106		N=121		N=45		N=458		
Patient interval													
Mean (SD)	33.6 (127.6)		48.0 (158.3)		26.8 (57.6)		24.0 (70.9)		27.4 (62.5)		31.2 (102.5)		0.13‡
Median (IQR)	10 (8)		10 (11)		10 (8)		10 (6)		10 (5)		10 (5)		
Last referral interval													
Mean (SD)	113.6 (188.4)		141.5 (179.1)		140.5 (184.8)		205.8 (221.8)		153.1 (174)		152.4 (196.4)		<0.001§‡
Median (IQR)	13 (173)		78 (245)		65 (204)		120 (327)		67.5 (279)		68.5 (240)		
Secondary care interval													
Mean (SD)	43.9 (90.2)		30.2 (34.7)		67.7 (104.7)		41.0 (51.9)		32.9 (27.2)		45.3 (75.0)		<0.001§‡
Median (IQR)	27 (32)		24 (34)		42.5 (49)		31 (35)		23 (34)		31 (36)		
Diagnostic interval													
Mean (SD)	157.5 (213.1)		171.7 (176.6)		208.5 (215.5)		246.9 (223.3)		186.5 (179.6)		197.9 (209.8)		<0.001§‡
Median (IQR)	55 (158)		110 (237)		128 (230)		167 (366)		99 (281.5)		110.5 (252)		
Until 60 days	61	55	27	36	28	26.4	29	24	15	33.3	160	34.9	<0.001§
>60 days	50	45	48	64	77	72.6	90	74.4	29	64.4	294	64.2	
Unknown	0	0	0	0	1	0.9	2	1.7	1	2.2	4	0.9	
Treatment interval													
Mean (SD)	152.3 (198.2)		177.8 (176.8)		215.7 (219.3)		263.4 (229.8)		192.6 (180.4)		204.2 (210.4)		<0.001§
Median (IQR)	57 (157)		117 (229)		131 (237)		174 (386)		128.5 (281.5)		121.5 (266)		
All patients	n=112		n=75		n=109		n=162		n=55		n=513		
Patient interval													
Mean (SD)	33.4 (127.1)		48.0 (158.3)		26.4 (56.8)		20.4 (61.5)		24.3 (56.8)		28.9 (97.1)		0.15‡
Median (IQR)	10.0 (7)		10.0 (11)		10.0 (8)		10.0 (0)		10.0 (3)		10.0 (3)		
Last referral interval													
Mean (SD)	112.6 (187.9)		141.5 (179.1)		138.8 (183.0)		205.5 (235.2)		137.5 (171.2)		152.2 (201.3)		<0.001§‡
Median (IQR)	12.5 (168)		78.0 (245)		64.0 (199.5)		117.0 (339)		56.0 (224)		64.0 (239)		
Secondary care interval													
Mean (SD)	43.8 (89.8)		30.2 (34.7)		66.8 (103.5)		45.1 (59.1)		32.0 (28.0)		45.9 (74.3)		<0.001§‡
Median (IQR)	27.0 (31.5)		24.0 (34)		42.0 (45)		32.0 (41)		23.0 (33)		31.0 (37)		

Continued

Table 3 Continued

Intervals*	Diagnostic pathway												
	Self-presentation to ED		Family physician referral to ED		Referral to elective gynaecology/oncogynecology from family physician		Referral to elective gynaecology/oncogynecology care from other specialist		Other/unknown		Total		P value†
	n	%	n	%	n	%	n	%	n	%	n	%	
Diagnostic interval													
Mean (SD)	156.4 (212.4)		171.7 (176.6)		206.0 (213.5)		216.3 (236.2)		155.6 (174.9)		187.9 (213.0)		0.018§‡
Median (IQR)	55.0 (155)		110.0 (237)		127.5 (225)		121.0 (319)		71.0 (237)		103.0 (243)		
≤60 days	62	55.4	27	36	29	26.6	56	34.6	24	43.6	198	38.6	0.002§
>60 days	50	44.6	48	64	79	72.5	104	64.2	30	54.5	311	60.6	
Unknown	0	0	0	0	1	0.9	2	1.2	1	1.8	4	0.8	
Treatment interval													
N, mean (SD)	151.3 (197.6)		177.8 (176.8)		213.0 (217.3)		263.7 (241.7)		177.0 (177.3)		204.2 (214.5)		<0.001§
Median (IQR)	56 (155)		117 (229)		129.5 (233)		173 (383)		101.0 (289)		117 (263)		

*Patient interval: between symptom onset and the first consultation (start point); last referral interval: between first consultation and the suspicion of a possible ovarian cancer; secondary care interval: between the suspicion of a possible ovarian cancer and the diagnosis; diagnostic interval: between the first consultation and confirmation of a diagnosis of ovarian cancer; treatment interval: between the first consultation and the first treatment (neoadjuvant chemotherapy or surgery).
†χ^2 test.
‡Kruskal-Wallis test.
§Statistical significance (p<0.05).
.ED, emergency department.

observed in the cohort as a whole (including asymptomatic patients) were similar.

At the end of follow-up, the rates of recurrence, disease progression and death were 45.6%, 28.1% and 48.1%, respectively (table 4). Median follow-up was 72 months, or 76 months in patients receiving elective care outside of family medicine. One-year survival was 92.4% and 5-year survival, 56.7%, with no significant difference between diagnostic pathways, although mortality at both time points was higher in the patients diagnosed through the emergency pathways.

Table 5 shows the variables included and the results of the multivariate Cox regression at one and 5 years' follow-up. In the Cox survival models, advanced tumour stage at the time of surgery was a significant risk factor both at 1 year (HR 3.84, 95% CI 1.23 to 12.02) and at 5 years (HR 5.36, 95% CI 3.07 to 9.36). The type of treatment received was also a significant risk factor, although the magnitude of the association decreased at 5 years' follow-up. Regarding age, the magnitude of the HR for 5-year survival increased with age.

In the multivariate Cox model, adjusted for age, AMG, stage and treatment, 5-year survival was higher in people who presented with gynaecological bleeding (HR 0.35, 95% CI 0.16 to 0.79; table 5; figure 2A). Patients whose first contact did not involve primary care had a slight disadvantage over other start point presentations (HR 1.39, 95% CI 0.93 to 2.09; table 5; figure 2B). Diagnostic pathways involving a referral to elective gynaecology/oncogynecology care from a specialist other than a family physician (HR 0.80, 95% CI 0.51 to 1.26) and self-presentation to emergency services (HR 0.82, 95% CI 0.52 to 1.31) also had a slight advantage over patients referred from family medicine (table 5; figure 2C), although the difference was not statistically significant.

Online supplemental file information 2 shows the variables included and the results of the univariate and multivariate Cox model.

DISCUSSION

Summary

Two out of three people treated surgically with a curative intent for EOC had initially reported their symptoms to their family physician. In symptomatic patients, the median diagnostic interval was 110.5 days, and this period was three times higher in those diagnosed through elective care other than family medicine vs emergency self-presentation. Survival to 1 year was 92.4% and to 5 years, 56.7%, with no significant differences between diagnostic pathways. In the Cox models, survival was influenced by advanced stage at 1 year (HR 3.84, 95% CI 1.23 to 12.02) and 5 years (HR 5.36, 95% CI 3.07 to 9.36), as was the type of treatment received, although this association was attenuated over follow-up. Age became significant at 5 years of follow. After adjusting for age, comorbidity, stage and treatment received, higher 5-year survival was associated with gynaecological symptoms (vaginal bleeding). Patients diagnosed through elective gynaecology/oncogynecology care from specialists other than a family physician and emergency self-presentation also showed slightly higher survival, as did people whose first contact was in primary care; however, these differences were not statistically significant.

Comparison with findings from other studies

Survival and prehospital factors in population cohort studies of ovarian cancer

We identified two population cohort studies based on medical registries, analysing survival from ovarian cancer according to prehospital factors, including diagnostic pathways. The first was the control (unscreened) cohort of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which included 574 cases diagnosed from 2001 to 2014,[19] and the second was the Manitoba Ovarian Cancer Outcomes cohort, involving 601 cases in Canada, diagnosed from 2004 to 2010.[20]

Our patients had some differences compared with the UKCTOCS cohort[19] with regard to their age (median 60.0 vs 62.7 years, respectively) as well as the proportion diagnosed at advanced stages (67.4% vs 75.9%), with type II tumours (66.9% vs 73.9%) and receiving neoadjuvant treatments (39.2% vs 19%) or interval surgery (38.6 vs 19.0%). A larger percentage of the Manitoba cohort was treated with primary surgery followed by adjuvant chemotherapy (49.5% vs 42.5%).[20]

The survival in these two cohorts,[19 20] as in ours, was influenced by age, advanced stage at diagnosis and type II histology, mostly represented by high-grade serous carcinoma and receiving neoadjuvant chemotherapy and interval surgery.

Diagnostic pathways

Different reviews are consistent in concluding that the emergency pathway is a predictive indicator of short-term mortality following a cancer diagnosis,[8–11] even after adjusting for age, stage and comorbidity.[9] Comparing diagnostic pathways between studies is not straightforward, as these depend on the healthcare model, the availability of fast referral circuits such as 2 weeks urgent referral (TWUR)[10] and the type of cancer.[8] In the context of a TWUR programme, an audit in Scotland[21] found that 31.6% of ovarian cancers are diagnosed through this pathway, while 37% were in the UKCTOCS cohort.[19] Having a TWUR programme modifies the diagnostic strategies followed by primary care physicians in patients with a suspicion of cancer.[22]

Our healthcare system, similar to that of the UK and Denmark with regard to the family physician's role as gatekeeper, does not have a TWUR programme for ovarian cancer, as reflected in the higher proportion of diagnoses in emergency services compared with the UKCTOCS study (36.4% vs 24%).[19] In the Manitoba study, where primary care does not serve as gatekeeper, approximately 28.4% of the patients presented to the ED.[20]

Table 4 Recurrence and progression during follow-up

	Diagnostic pathway												
	Self-presentation to ED (N=112)		Family physician referral to ED (N=75)		Referral to elective gynaecology/oncogynecology from family physician (N=109)		Referral to elective gynaecology/ oncogynecology care from other specialist (N=162)		Other/ unknown (N=55)		Total (N=513)		
Outcomes	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**P value***
Recurrence	62	55.4	31	41.3	46	42.2	68	42	27	49.1	234	45.6	0.17
Progression													
Yes	40	35.7	25	33.3	27	24.8	36	22.2	16	29.1	144	28.1	0.084
Unknown	3	2.7	4	5.3	0	0	4	2.5	2	3.6	13	2.5	
Mortality													
No	48	42.9	34	45.3	60	55	94	58	24	43.6	260	50.7	0.13
Yes	63	56.3	39	52	47	43.1	68	42	30	54.5	247	48.1	
Lost to follow-up	1	0.9	2	2.7	2	1.8	0	0	1	1.8	6	1.2	
Length of follow-up (months)†													
N, mean (SD)	54.1 (29.5)		53.2 (29.3)		61.1 (26.9)		63.0 (27.3)		54.1 (28.2)		58.3 (28.3)		0.010‡§
Median (IQR)	62.5 (54.5)		59.0 (57.0)		73.0 (44.0)		76.0 (47.0)		55.0 (55.0)		72.0 (51.0)		
One-year survival													
Survived	100	89.3	67	89.3	103	94.5	155	95.7	49	89.1	474	92.4	0.28
Dead	11	9.8	6	8	4	3.7	7	4.3	5	9.1	33	6.4	
Lost to follow-up	1	0.9	2	2.7	2	1.8	0	0	1	1.8	6	1.2	
Five-year survival													
Survived	59	52.7	37	49.3	67	61.5	102	63	26	47.3	291	56.7	0.18
Dead	52	46.4	36	48	40	36.7	60	37	28	50.9	216	42.1	
Lost to follow-up	1	0.9	2	2.7	2	1.8	0	0	1	1.8	6	1.2	

*P value: χ^2 test.
†Months from the date to diagnosis to the date of death o last entry on the medical chart.
‡Statistical significance (p<0.05).
§Kruskal-Wallis test.
ED, emergency department.

Table 5 Multivariate Cox analysis of mortality at 1 and 5 years of follow-up

	1-year follow-up multivariate Cox regression			5-year follow-up multivariate Cox regression		
Variables	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age (years, categorical)						
<50 (N=98)	1		0.69	1		0.008*
50–59 (N=144)	0.61	0.16 to 2.30	0.46	1.91	1.09 to 3.35	0.023*
60–69 (N=144)	0.65	0.17 to 2.57	0.54	2.08	1.19 to 3.64	0.010*
≥70 (N=127)	0.99	0.26 to 3.70	0.99	2.74	1.54 to 4.88	<0.001*
Stage						
I–II (N=167)	1			1		
III–IV (N=346)	3.84	1.23 to 12.02	0.021*	5.36	3.07 to 9.36	<0.001*
Histological group						
Type II (N=343)	1			1		
Type I (N=170)	1.03	0.40 to 2.63	0.95	1.19	0.78 to 1.82	0.41
Symptomatic profiles						
Asymptomatic (N=55)	1		0.26	1		0.020*
Nonspecific symptoms (N=274)	0.27	0.06 to 1.14	0.076	0.94	0.52 to 1.70	0.84
Gynaecological symptoms (vaginal bleeding) (N=70)	0.00	.	0.96	0.35	0.16 to 0.79	0.011*
Signs associated with advanced disease (N=114)	0.49	0.11 to 2.10	0.34	1.01	0.56 to 1.83	0.97
Start point						
Primary care (N=384)	1			1		
Other (N=129)	0.96	0.33 to 2.79	0.94	1.39	0.93 to 2.09	0.11
End point						
Family medicine referral to ED (N=75)	1		0.34	1		0.84
Self-presentation to ED (N=112)	1.73	0.55 to 5.43	0.35	0.82	0.52 to 1.31	0.42
Referral to elective gynaecology/ oncogynecology care from family medicine (N=109)	0.54	0.15 to 2.02	0.36	0.96	0.60 to 1.53	0.86
Referral to elective gynaecology/ oncogynecology care from other specialist (N=162)	0.62	0.17 to 2.25	0.47	0.80	0.51 to 1.26	0.33
Other/unknown (N=55)	1.19	0.29 to 4.91	0.81	0.90	0.52 to 1.55	0.69
Treatment received						
Surgery +adjuvant therapy (N=254)	1		<0.001*	1		<0.01 *
Surgery alone (N=58)	11.29	3.11 to 41.03	<0.001*	2.21	1.21 to 4.06	0.010*
Neoadjuvant therapy +surgery (N=23)	5.45	1.47 to 20.26	0.011*	2.65	1.49 to 4.70	<0.001*
Neoadjuvant therapy +surgery + adjuvant therapy (N=178)	1.25	0.43 to 3.65	0.69 ns	2.05	1.43 to 2.94	<0.001*
Diagnostic interval						
Until 60 days (N=198)	1		0.010*	1		0.091
> 60 days (N = 311)	1.03	0.44 to 2.42	0.95	1.00	0.73 to 1.38	0.99
Unknown (N = 4)	46.15	3.78 to 564.19	0.003*	5.12	1.17 to 22.36	0.030*

*Statistical significance (p<0.05).
AMG, adjusted morbidity groups; ED, emergency department.;

Few studies describe the use of healthcare services in cases of ovarian cancer that are not emergencies. In our study, 25% of the patients diagnosed in the ED had not had any prior contact with their family physician. Among those who had, 21.7% were referred to the ED by their family doctor, and 18.3% went on their own initiative, either while waiting for an appointment in secondary care or because their family doctor missed the opportunity to make the correct diagnosis. Similarly, 23.4% of the UKCTOCS cohort were referred to the ED by their general practitioner.[19] In agreement with Murchie, we believe that in the absence of adequate rapid referral routes, the ED is an effective pathway to diagnosis in people with advanced disease.[23]

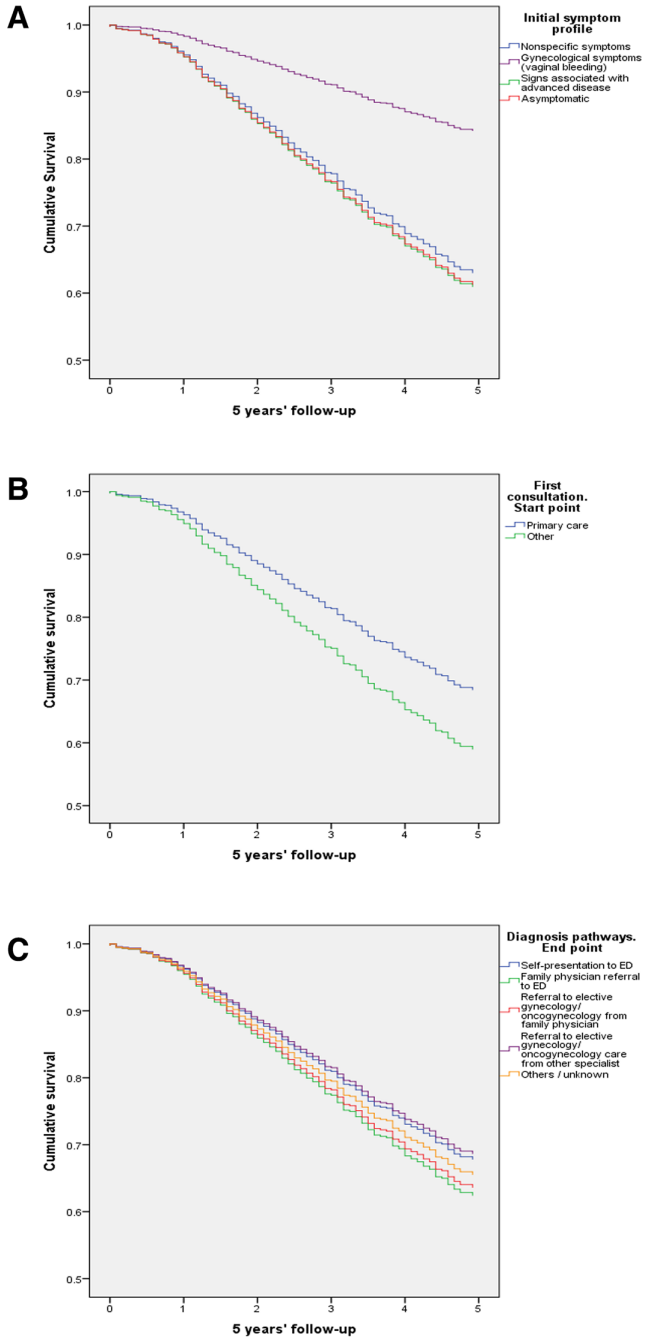

Figure 2 Survival functions according to symptomatic profiles (A), first consultation (start point) (B) and diagnostic routes (end point) (C). ED, emergency department.

In our study, we observed slightly better 1-year survival in people diagnosed through elective physicians, whether in family medicine (94.5%) or other specialties (95.7%), compared with diagnoses received in the ED (89.3% in both). These differences were maintained at 5 years. Our survival rates in the emergency pathways were notably higher than those reported in the UKCTOCS cohort[19] or other studies[8 24]; however, due to selection bias these results are not comparable.

Our study does not provide evidence about whether gatekeeper health systems result in lower 1-year survival.[3 6] Nevertheless, and overturning our expectation, its results do show that when primary care is involved (74.9% of the cases), 1-year survival is slightly higher, a trend which is discreetly more evident at 5 years.

Symptoms at presentation

Clinical practice guidelines for ovarian cancer differ in the symptoms they describe.[25] American guidelines, influenced by the ovarian cancer symptom index,[16] define a short list of symptoms that are most likely to be caused by ovarian cancer: abdominal or pelvic pain, abdominal distension or swelling, and feelings of early satiety or difficulty eating.[26] NICE guidelines[17] include other symptoms that have not shown a clear association: fatigue, back pain and urinary symptoms.[26] When we designed our study, we did not have our own guidelines to follow, so we identified all the signs and symptoms most commonly included in other available guidelines.

Similarly to the UKCTOCS[19] and Manitoba[20] cohorts, 83.9% of our patients presented symptoms. Compared with the UKCTOCS cohort,[19] our patients presented more frequently with abdominal/pelvic pain (46.4% vs 39.5%) and less frequently with abdominal distension (15.0% vs 39.2%), changes in bowel movements (14.0% vs 20.0%), and loss of appetite (3.7% vs 14.6%). These differences may be due to under-recording of initial symptoms, which may have been considered trivial, and to the definitions used. The English 'abdominal distension' is more accurate than the Spanish equivalent, encompassing the feeling of distension plus an increase in abdominal circumference (clinical sign for examination) as well as the term 'bloating'. A higher proportion of patients presented with anomalous vaginal bleeding in our study (14.4%) compared with the UKCTOCS (7.4%)[19] and Manitoba (9.8%)[20] cohorts as well.

In the UKCTOCS cohort, the presenting symptoms associated with lower survival were abdominal pain, loss of appetite, feelings of early satiety and (non-significantly) abdominal distension.[19] As with our and the Manitoba cohorts,[20] the British study also showed better survival in patients presenting with vaginal bleeding; in our study, this difference was significant.

Diagnostic intervals

There is a widespread perception among healthcare professionals that prolonged diagnostic intervals have an impact on cancer survival.[27] However, for ovarian cancer, evidence supporting this hypothesis is scarce and does not confirm such an association.[28]

In our cohort, the diagnostic interval in symptomatic patients is longer than that of other studies (110.5 days), although our results are not directly comparable with others due to differences in health system model and the absence of a TWUR programme. In the UKCTOCS study, the median diagnostic interval for 55% of the cohort was 80 days: 91 days at early stages and 75 days at advanced stages.[19] In Manitoba, these intervals were shorter: 77 days at early stages and just 27 in patients with advanced disease.[20] In the Cancer Benchmarking

Partnership (ICBP) study, it was approximately 48 days.[29] In the patients included in our study who were diagnosed via elective care from specialists other than family medicine, the diagnostic interval was much longer, 167 days, in part because a benign pathology was suspected, and malignance was only confirmed after analysing the surgical specimen.

The length of the diagnostic interval is not always a good prognostic indicator, as the presence of a more aggressive tumour or more advanced disease may accelerate presentation and subsequent investigation.[10 30 31] However, as seen in the Manitoba cohort, in tumours with an advanced stage, a diagnostic interval of 80 days or less is significantly associated with better survival.[20] At the same time, cancers found incidentally, with no diagnostic interval, show better survival at 5 years.[20] In our study, these cases show only a discreet advantage in 1-year survival.

Other registry studies,[19 30 31] interviews[32] and patient questionnaires[33] have likewise failed to demonstrate an association between diagnostic delay and survival in ovarian cancer. Yet, reducing the length of this interval should be a priority objective, as prolonged intervals tend to be associated with worse quality of life and patient satisfaction.[19]

Implications

Given the high rate of participation by primary care in the process for diagnosing ovarian cancer, the implementation of specific or multidisciplinary rapid diagnostic pathways would constitute a good opportunity to improve early diagnosis of ovarian cancer in Catalonia.

Building capacity in primary care for the recognition of the signs and symptoms of ovarian cancer and training clinicians in the use of transvaginal ultrasound would also be important, as would updating and improving professional skills in gynaecology and reducing the length of waiting lists for surgical treatment of benign ovarian pathologies.

Strengths and limitations

This is a retrospective, quasi-population-based cohort study in people with EOC, performed within the framework of a clinical audit of medical records in primary and hospital care. The cohort does not include borderline tumours or others that were not treated with curative-intent surgery. In Catalonia, there are an estimated 486 new cases of ovarian cancer per year[34]; our study encompasses 513 cases diagnosed over 2 full years, approximately half the expected incidence. We do not know how many cases that were not included in our cohort were treated in private hospitals or how many received other types of treatments.

Most studies evaluate factors influencing survival in ovarian cancer and audit the results and the adherence to treatment standards, without considering the contribution of prehospital factors that could affect survival. Our study links data from primary, secondary and hospital care along with mortality registries, information that has enabled us to synthesise and describe the diagnostic process, from the start of the first initial symptoms until death or last follow-up. The use of these different sources also enabled us to contrast the available clinical and administrative information.

In all cases, data were available on the classification by stage, treatments received, and follow-up. With regard to the patient profile, we did not have information on possible confounders, such as socioeconomic status. To group people according to comorbidities, we used the AMG[15] rather than the classical Charlson index.[35] The presence of gene mutations related to ovarian cancer is under-recorded, as systematic genetic studies were implemented only after the beginning of the study. We cannot rule out the risk of information biases that could distort some estimations (given the different interactions between variables as well as possible measurement errors, it is unsurprising that survival is not statistically associated with prehospital healthcare); however, several studies report that data from the e-CAP the primary care electronic health records, including cancer diagnoses, show a good level of registry and coding and are of sufficient quality to perform research.[36 37]

Few studies have investigated the relationship between diagnostic pathways for ovarian cancer and 1-year and 5-year survival, and this is the first such study to be performed in our setting. Studying diagnostic pathways in ovarian cancer is complex due to the characteristics of the initial symptoms on presentation, which are often numerous and vague, and to the coexistence of comorbidities.[38] In that sense, the definition of the diagnostic pathway using contextual criteria, based on administrative data, simplifies and standardises the classification.[11]

Currently, there is growing interest in measuring and comparing diagnostic intervals in cancer and evaluating their impact on survival. The Aarhus Statement facilitates a methodology to evaluate the intervals. However, the intervals in primary care could be affected by the characteristics of the healthcare model as well as by the data collection methods, the under-recording of symptoms, and the presence of other symptoms unrelated to ovarian cancer.[29 39]

Given the characteristics of ovarian cancer, our conclusions could probably be generalised to other settings and models, at least in part, as most of the factors identified are not specific to our healthcare model.

CONCLUSIONS

The limited impact of diverse factors associated with the prehospital phase, and the similarity of the results in different diagnostic pathways suggests that survival in ovarian cancer depends above all on the stage at diagnosis, administration of primary cytoreduction plus chemotherapy and patient age. Diagnosis in emergency services, in the absence of a rapid diagnostic circuit for

ovarian cancer, may be an opportunity to improve early diagnosis in primary care.

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Contributors Conceptualisation—ideas; formulation or evolution of overarching research goals and aims (MM-C, CV-V, PM-W, JMB). Data curation—management activities (MM-C, CV-V, PM-W, LA). Formal analysis—analysis or synthesis of study data (LA, PM-W). Funding acquisition—acquisition of the financial support for the project leading to this publication (MM-C, CV-V, LA, PM-W, JMB). Investigation—conduct of research and investigation process, specifically performing the experiments or data/evidence collection (MM-C, CV-V). Methodology—development or design of methodology; creation of models (PM-W; LA). Project administration—management and coordination responsibility for the research activity planning and execution (MM-C). Supervision—oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team (JMB, MM-C). Validation—verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs (NCB, MH). Visualisation—preparation, creation and/or presentation of the published work, specifically visualisation/data presentation (all) Writing—original draft—preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation) (MM-C, CV-V, LA, PM-W). Writing—review and editing—preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision—including prepublication or postpublication stages (all). The guarantor (JMB) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

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